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# PROCEEDINGS OF THE AIR POLLUTION RESEARCH PLANNING SEMINAR (2ND) FEBRUARY 3-7, 1958 HELD IN CINCINNATI, OHIO

Robert A. Taft Sanitary Engineering Center
Cincinnati, Ohio

1958

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# PROCEEDINGS

of the

# SECOND AIR POLLUTION RESEARCH PLANNING SEMINAR

February 3-7, 1958

Cincinnati, Ohio

U. S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service

324

# PREFACE

This document records the results of the Second Seminar on Air Pollution Research Planning sponsored by the Public Health Service and held at the Robert A. Taft Sanitary Engineering Center, Cincinnati, Ohio, on February 3-7, 1958.

Attendance was by invitation. The objectives of the Seminar were to:

1) Assess the current status of air pollution research.

2) Bring to light areas of both over- and under emphasis.

3) Compare criteria now being used in problem selection.

4) Promote the exchange of ideas among air pollution research administrators.

5) Improve contacts between sponsoring organizations and researchers.

6) Pool information on various other facets of air pollution research activity.

Minutes of the medical sessions are recorded in full. For the engineering and physical sciences sessions final committee reports only are recorded. Proceedings of medical sessions were edited by Dr. Harry Heimann, Chief, Operational Research Section, Air Pollution Medical Program, Division of Special Health Services. Proceedings of the engineering and physical sciences sessions were edited by Donald M. Keagy, Sanitary Engineer, Sanitary Engineering Center.

This document has been printed in small quantity for a specific use, and should not be listed in journals or current reading lists as being available on request.

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# PROCEEDINGS

DR. HEIMANN: The purpose of our sessions is to discuss in an informal manner among ourselves how far we have gone in the biological studies of air pollution in this country. For that purpose we have asked various people who have been working in the field to come here to tell us what they have been doing. We are indeed grateful that so many of you have been willing to cooperate with us, the Air Pollution Medical Program of the Public Health Service. We also asked a second group of people to be at the meeting as commentators. Finally, there is a third group present that is here only to listen and learn.

A stenotypist will record what will be said at the meeting. There will be a transcription of his notes, and these will be duplicated in a limited number of copies for distribution to all persons attending the meeting and a few other interested people. You will be given an opportunity to correct the transcript of what you may say here.

The program of our meeting is divided into seven different panels that will run consecutively. Each panel has its own chairman who has accepted the responsibility of running his section of the meeting and of preparing a review of what his panel covers, for Wednesday morning. This review is meant partly for ourselves and partly for the engineering groups who will be in on Wednesday morning to hear what we will have covered. Their own meetings begin on Wednesday afternoon.

Dr. Hayes is Chairman of Panel #I.

## PANEL I

## THE EFFECTS OF AIR POLLUTANTS UPON ENZYME SYSTEMS, CELL CULTURES, AND TISSUES

DR. HAYES: Dr. Gast, who worked with Dr. Estes will present the first paper entitled, "An Approach To The Experimental Evaluation Of The Biochemical Effects Of Air Pollutants."

DR. GAST: Inhibition of metabolism has long been recognized in the bacteriostatic and bactericidal effects of antiseptics and antibiotics. This theme has been carried over into the study of anti-metabolites in mammalian tissues and organs. The classical techniques of industrial hygiene and toxicology have, however, neglected this approach. The mode and site of action of trace concentrations of toxic or irritant substances at the cellular and subcellular levels should, it seemed to us, provide the clues and tools to magnify the physiological events resulting from specific chemical reactions. This should make it possible to predict and to study the dynamic phenomena which precede the morphological changes seen in disease and death of the organism.

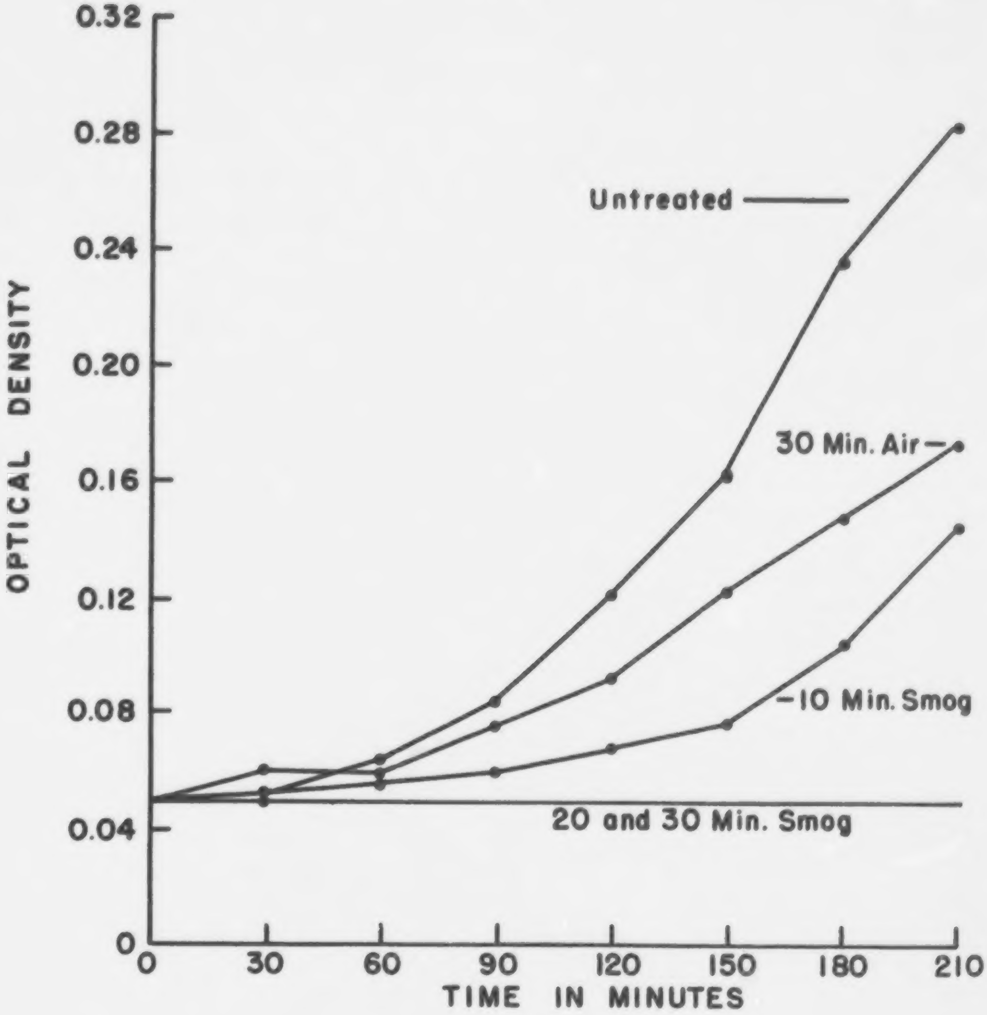
Before attempting to attack the study of the specific effects of an agent on enzyme systems either in vivo or in vitro, it is important to know that the general effects observed are real, and arise from the specific cellular components studied. The parameters which we have utilized for this purpose are: 1) cell respiration, 2) oxygen consumption, 3) growth, 4) irritability, and 5) metabolite incorporation. Because of time limitations this report will be confined to the biochemical changes observed following brief exposures of E. coli and of leucocytes to both irradiated and unirradiated simulated oxidant type of air pollution mixtures. Controls included unexposed cells similarly handled, and cells exposed to air, and to unirradiated but heated mixtures of nitrogen oxides and hydrocarbons. Two types of exposure chambers were used to provide thin layers of cells in appropriate media.

In Figure I the effect of exposure of E. coli on growth can be seen. Following rapid growth for four hours, the organisms were then "sensitized" by permitting a four-hour incubation period without aeration. The exposure times have

2-a

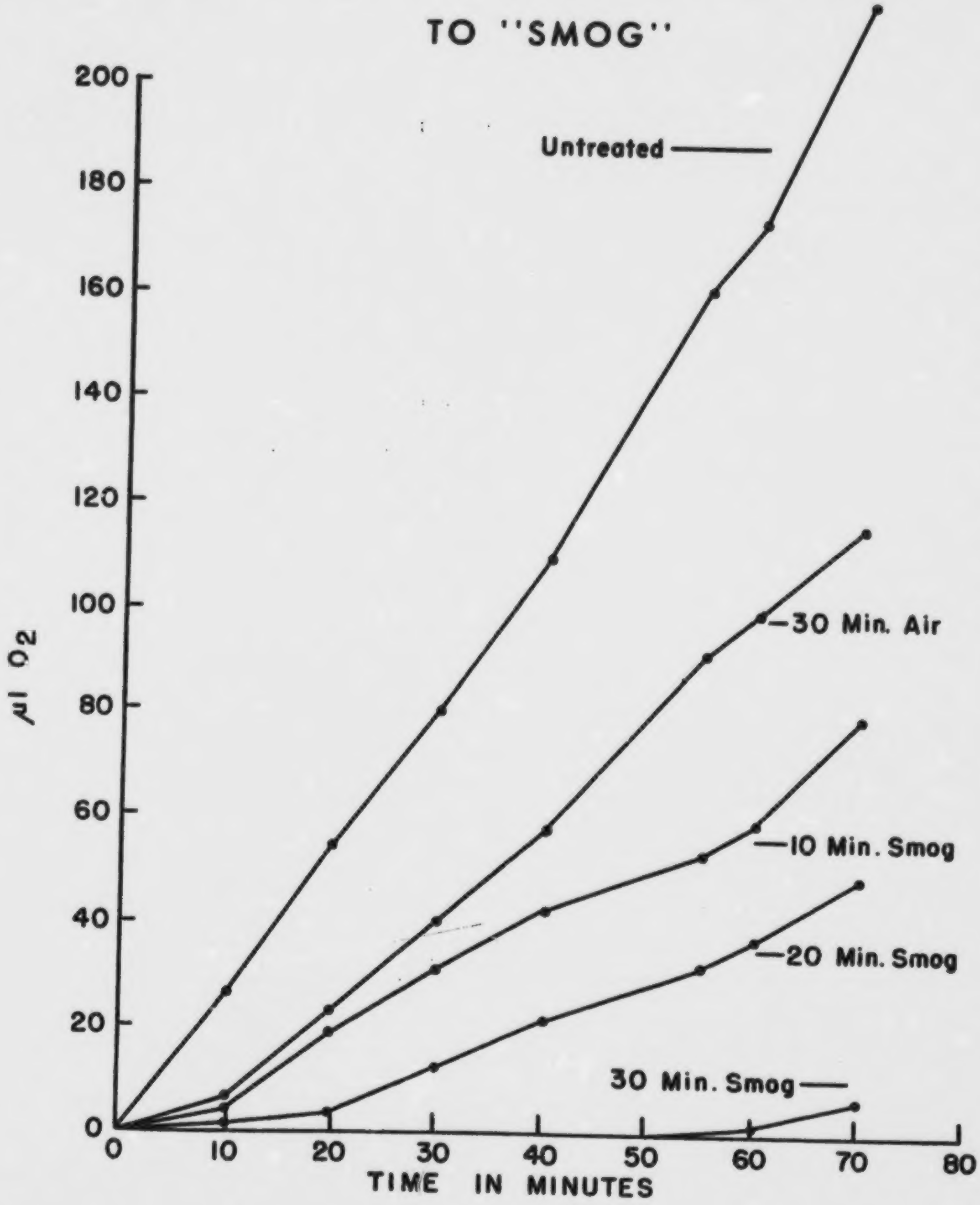
# GROWTH RESPONSE OF "ATTENUATED" E.COLI

## COMPARISON OF VARYING TIMES OF EXPOSURE TO "SMOG"



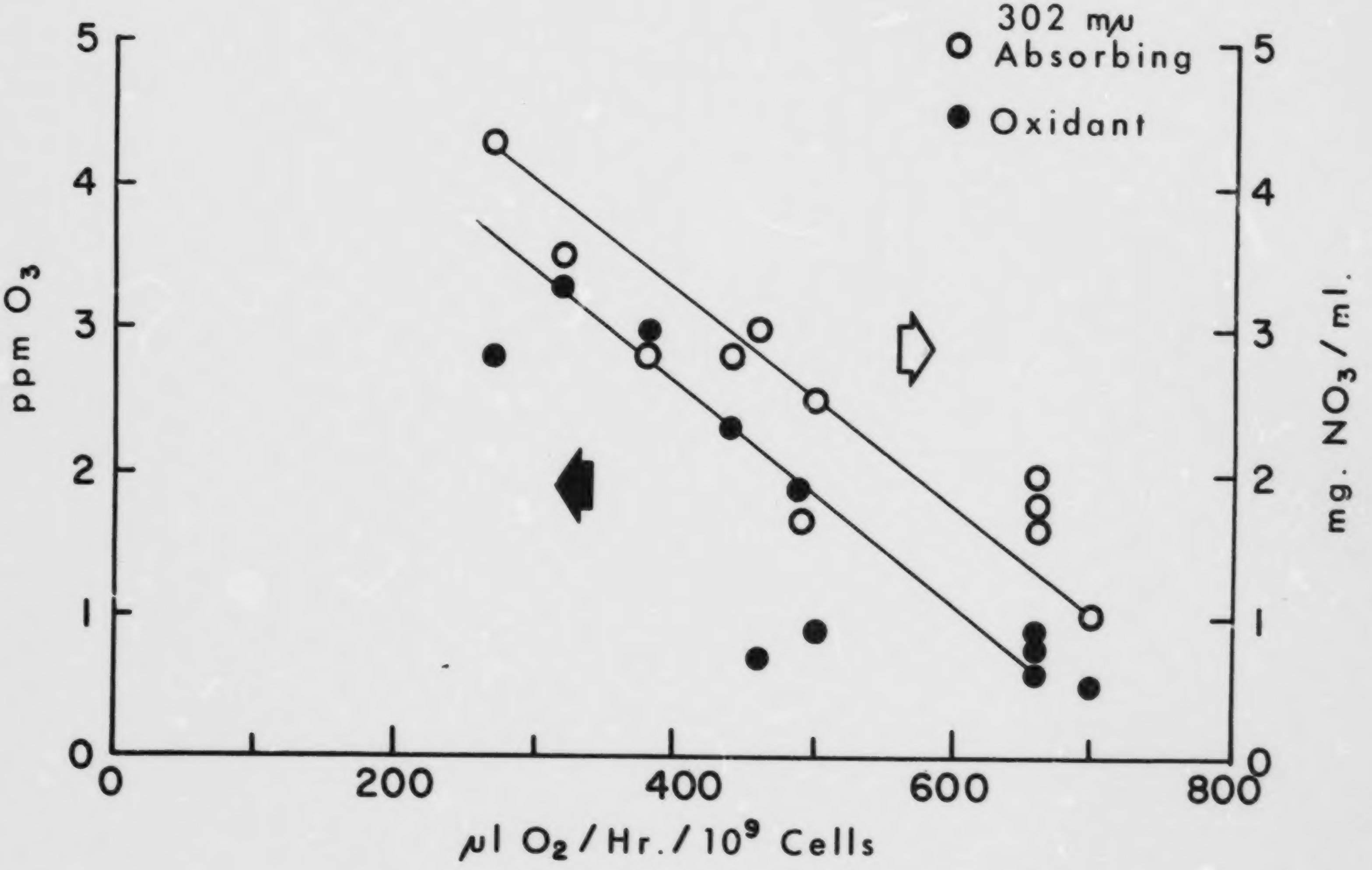
# OXYGEN UPTAKE OF "ATTENUATED" E.COLI

## EFFECT OF VARYING TIMES OF EXPOSURE TO "SMOG"



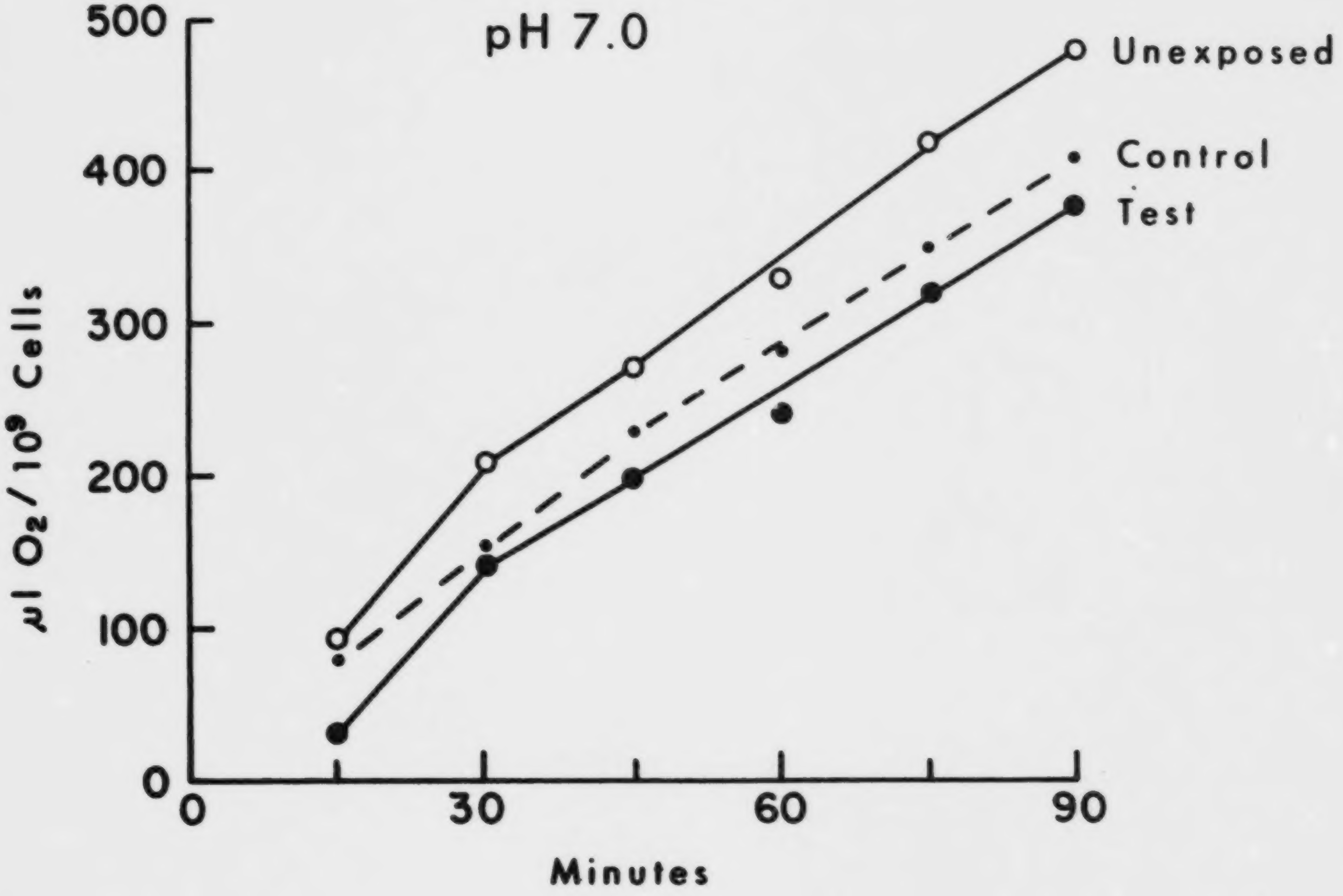
2-C

# OXYGEN CONSUMPTION VS.
# CONCENTRATION OF COMPONENTS



a-d

# EFFECT OF BUFFER SOLUBLE POLLUTANTS



been 15 minutes, or, as shown on the illustration. Compared to the "unsensitized" cells the effect of unaerated incubation on growth will be seen in the curve marked "30 minutes of air."

The upper curve represents the untreated cells. The next curve shows those that have been exposed to air, then to the ten-minute exposure to pollutants, as well as the 20 and 30-minute exposures, which resulted in death of the organisms. Figure II shows the effect on oxygen consumption. Again the upper curve is that of the untreated cells. The next one shows result of the 30-minute exposure to air. Notice the progressive decrease of oxygen consumption in the 10, 20, and 30-minute exposures to the pollutants.

A similar depression of oxygen consumption has been observed on polymorphonuclear leucocytes. In an attempt to correlate these data with analyses of the pollutants, it would appear that oxidants -- as determined by the phenolphthalein method -- and the ultraviolet absorbing materials -- arbitrarily expressed as nitrates -- are inhibitory.

Figure III will show the effect on oxygen consumption of polymorphonuclear leucocytes compared with the concentrations of the components. From these data, it is difficult to indict either oxidants or nitrogen-containing components alone. Indeed, they actually could be supplementing each other, or represent different methods of measuring the same unidentified materials.

A similar inhibition of oxygen consumption was observed when the cells were suspended in buffered salt solution into which the pollutant and control mixtures had been bubbled. This method of testing is shown in Figure IV. We have called this "indirect exposure." The upper curve shows the oxygen consumption of cells not exposed to the pollutants, but which were otherwise handled similarly. The second curve, marked "control," shows the oxygen consumption of cells exposed to the unirradiated pollutant mixture; while the lower curve shows those cells exposed to the irradiated pollutant mixture. It is apparent from these experiments that we are dealing with materials which are stable or active for at least 30 minutes, because this is the length of time required for the collection of the soluble pollutants. When leucocytes are exposed to aliphatic nitro-compounds, such as nitro-methane or -ethane, the oxygen consumption is similarly inhibited. This inhibition is observed with pure compounds in the range of 1 to 2 parts per million. However, the corresponding alcohols at comparable concentrations have no effect on the oxygen consumption; nor do the inorganic nitrates or nitrites have an effect. Thus, it appears that the observed inhibition is due to the nitro-paraffins, *per se*.

At present these observations cannot be translated in terms of the whole organism and they do not point to specific chemical reactions. However, they do represent positive evidence of a general biochemical effect induced by brief exposures to simulated oxidant type pollutants, and we believe that these results appear to warrant further study, and to be a useful and sensitive adjuvant to present techniques of industrial hygiene and toxicology.

DR. HAYES: Dr. Hodge, would you care to comment?

DR. HODGE: These are very interesting results, Dr. Gast. I am completely sympathetic with your idea that we can use the effects that are seen in microorganisms or in cells as indices. We found this to be very useful in working out some of the details of the mechanism of uranium poisoning, for example. This is a powerful technique, and as fast as the biochemists and microbiologists tell us something about how cells work, and we find a detectable effect, we can start determining how this effect is induced.

I hope you won't mind if I tell you that when you mark the word "control" on your slide, and this control was an exposure to a non-irradiated complicated mixture, it is very confusing. I wish you would save the word "control" for something besides the exposure groups.

You get an effect by exposure to air alone. What is it in the ambient air that is doing this? Is this some undetected smog in our ambient air?

DR. GAST: Untreated cells were shown first. These were the cells that were not "sensitized" by an additional incubation period. The air exposure happens to be a positive control of the "sensitized" cells. In other words, that is the maximum response of which the cells are capable after they have been sensitized.

We have found this necessary on E. coli at that particular stage, because they are very virile organisms, when it comes to both growth and oxygen uptake; in order to make them sensitive, we have had to "hit them over the head," and the air control there is a positive control. I am sorry about this word, "control." It happens to be the only word I can think of using. We have all kinds of control, and we have felt that it is essential to find out whether there is present in the mixture any effective agent that has not been produced by irradiation. When we are studying the effect of irradiation, that's why we have this "negative control" of the agents themselves that have been heated, but not irradiated.

DR. HAYES: I think it might help the group if you would explain what "sensitized" means.

DR. GAST: I wish I could. I have used the word "attenuated" at times. I don't know that it is any better. It represents an additional incubation period of about four hours without aeration. That's all I can tell you. What has happened to the cells, I don't know. I have tried bubbling nitrogen through the cultures and doing an anaerobic incubation. I have tried other things also. It doesn't seem to have the same effect. It is quite similar to placing the cells in the icebox for 48 or 72 hours.

DR. HAYES: In other words, it is necessary to cripple these things, in order to later demonstrate the effect of the pollutants?

DR. GAST: Yes. Possibly analogous to the way humans behave in exposures in the recorded acute air pollution episodes.

DR. HODGE: I have one other question I would like to ask Dr. Gast. I am not sure that I visualize his experiment clearly enough, that this is really an applicable question. We have used a gadget called, I think, the "biostat," invented by Leo Saillard, a physicist. He decided that if the biologists wanted a standard preparation of cells, they should theoretically be able to obtain such a preparation. So he invented this gadget called the "biostat" which produces cells of any specification that you wish. In this way one can have starved cells, old cells, young cells, or potassium-deficient cells, etc. You write the specifications, and it produces them for you. Is this something that is applicable to your research?

DR. GAST: It might be. There have been several techniques advocated for getting uniform cells. Some work has been done recently on protein formation with a similar technique. We were forced to find a technique in which the cells would respond to the pollutants, and we took the first one that we could find. Frankly, it is an opportunistic and empirical method. I haven't tried the biostat.

DR. GOLDSMITH: I wonder if you could tell us what the concentrations were of the substances which you were using to expose these cells?

DR. GAST: For the white cells, directly exposed, these were shown in Figure III. For the E. coli, it generally would run between one and a half and three and a half parts per million of oxidants, measured by the phenolphthalein method; and the ultraviolet absorbing materials expressed as nitrates are between one and a half and three and a half milligrams per liter. This, we recognize, is higher than the realistic concentrations.

DR. GOLDSMITH: What was the substance that you irradiated?

DR. GAST: The mixture of hydrocarbons was about 65 percent olefins and nitrogen oxides prepared from nitric acid and air.

DR. CHAMBERS: Dr. Gast, I think there is something in what you just said that may be critical -- your statement that these mixtures initially contained around 60 percent olefins, which I think may, in view of other evidence, be very significant. Could you say anything about how a mixture of this type in the absence of olefins would behave, in contrast with this mixture?

DR. GAST: We haven't tested that yet, Dr. Chambers. The only evidence we have so far is what I mentioned with respect to the nitro-paraffins. At concentrations of one to two parts per million, they also decrease the oxygen consumption. This is as far as we have gotten on our checking of the compounds. We started directly with pure compounds. We don't have any nitro alkenes yet. We hope to get some.

DR. SILVERMAN: From your concentrations of $NO_2$ I calculate something like 150 parts per million, which is pretty "stiff" as a dose for this gas. Is this right?

DR. GAST: 150?

DR. SILVERMAN: You said one and a half milligrams per liter.

DR. GAST: That is calculated as sodium nitrate, which we use for standardization. It actually represents the ultra-violet absorption, the optical density, at the same wave length at which nitrate absorbs.

DR. SILVERMAN: Well, I am going on the basis of one and a half milligrams per liter of nitrate, which is obviously a thousand times that in milligrams per cubic meter, without converting to volume equivalent. And these levels are roughly a thousand times smog levels, or more.

DR. GAST: I don't think it can quite be that high, Dr. Silverman, because we get similar effects with nitro-methane and nitro-ethane. So it doesn't seem that we would be getting such slight effects from the pollutants. Furthermore, we have in some cases almost the same concentrations in our "control," unirradiated mixture. And you don't get the same effect you do from the irradiated mixture.

DR. SILVERMAN: Well, of course, oxides of nitrogen are not very rapidly absorbed in bubbling through aqueous solutions.

DR. GAST: That's true; but, you see, you have the cell exposed in a thin layer just the same as you do in the lungs.

DR. SILVERMAN: The only thing that disturbs me, as I said in the beginning, is that the concentrations were very rich.

DR. GAST: Yes.

DR. HAYES: We can take one more question quickly.

DR. STOKINGER: I am not quite clear on the statement about nitro-alkenes, if you have 60 percent unsaturates in the mixture.

DR. GAST: That was a separate experiment, in which we placed the nitro-methane or the nitro-ethane in contact with the cells in the medium, and then measured the oxygen uptake.

DR. STOKINGER: I assume you have unsaturated nitro groups in your smog.

DR. GAST: We start with them, in a mixture. What we end up with, I don't know. We have the conventional method of analysis, and we have our ultraviolet analysis. We are working on other techniques.

DR. HAYES: If we have time later, we will continue the discussion. The next paper will be presented by Dr. Donald M. Pace, "The Action Of Known And Suspected Air Pollutants Of The Hydro-Carbon-Nitrogen Oxide Type Upon Tissue Cultures *In Vitro*, Second Interim Report."

DR. PACE: At last year's seminar, I reported on our studies on the effects of sulfur dioxide and nitrogen dioxide on certain tissue cells -- Earle's strain L, a liver strain, and the HeLa strain. Some of you will recall that we used various concentrations of these gases. The desired concentrations were obtained by passing the gas and air mixture through metering devices, using a chamber similar to that used by Dr. Svirbely.

For the most part, we used Carrel flasks for cultivating the cells, and a measured amount of nutrient medium (one milliliter) in each. Usually, the cultures are allowed to adjust by placing them in the incubator for three days before beginning the tests. We replace the fluid with fresh medium and then gas them. In early experiments, we used a 40-40-20 medium, in other words 40 parts horse serum, 40 parts saline, and 20 parts chick embryo extract. Recently we did away with the chick embryo extract and most of the horse serum, and are now using a synthetic medium plus a small amount of horse serum. The medium is changed every two days, and if there are gases to be added they are re-gassed at the same time; counts are also made at this time.

Last year's results indicated that the cells are more tolerant to nitrogen dioxide than to sulfur dioxide. There is an inhibition of proliferation in the lower concentration of sulfur dioxide whereas much greater concentrations of nitrogen dioxide were tolerated. We find that these cells still grow in 1500 ppm. nitrogen dioxide but not in this concentration of sulfur dioxide. The medium surrounding the cell, although thin, comes in contact with the gas. However, compared to a mucous membrane of the lung it is a fairly thick layer. So, whatever happens to the gas before it actually gets to the cell, is not known.

For this reason we proceeded to study the effects of the salts of these gases on various types of cells. This was done by dissolving the proper amount of sodium bisulphite, sodium sulphite, and sodium sulphate as salts of $SO_2$ and as sodium nitrate, and sodium nitrite as salts of $NO_2$. Concentrations of the salts used were 200, 100, 50, and 10 milligrams percent. All the studies in the series were carried out with a synthetic medium, plus 10 percent horse serum.

The results obtained are rather interesting. All the concentrations of sodium bisulphite used were toxic to the HeLa strain cells. This effect was less evident on the L strain, and least evident on liver cells. The liver cells seem to be able to tolerate as much as 50 milligrams percent of sodium bisulphate though growth certainly lagged as compared to that of the L cell. Sodium sulphite also affected the growth and proliferation of these cells adversely. The HeLa cells especially were killed in all concentrations. Again, the liver cell was more tolerant to these concentrations than the HeLa or the L strain.

The first slide shows the HeLa strain cells after five days. The second slide shows the effect of 100 milligrams percent of sodium bisulphite. The cells are dying, if not already dead.

The next slide illustrates the control. You can make out the spindle-shaped cells. These are fibroblasts; strain L cells. The next slide shows the same in sodium nitrate, 50 milligrams percent. So, although nitrate is not especially toxic, the nitrite seems to be quite toxic.

Recently we began our studies on the effect of ozone on the various clone cultures. Our preliminary work on this has been centered on learning the concentration of ozone that we should employ and one of the first cell lines tested was the strain L. We started off with a high concentration of 900 ppm. We also tried 150 ppm. These concentrations were chosen arbitrarily, and we exposed the cells to them. The higher concentration, of course, killed them. With the 150 milligrams percent, they died within a few days. The results are shown in the slides. These are results obtained with high concentrations. It is quite effective, in spite of the fact that it has to go through a fairly thick medium before it reaches the cells. At present we are testing much lower concentrations of ozone. We are continuing with the L strain and have added a human skin clone to the other cell types. We also have started investigations on the effects of various hydrocarbons on different cell types. The results are very sketchy up to date.

Later we hope to continue with our gassing methods, but, in the meantime, tests have been run by dissolving liquid hydrocarbons, such as 2-n-hexene, in the medium. It is difficult to ascertain the solubility of these substances in the medium. All we can say thus far is that we have a 100 percent saturated, a 50 percent saturated, or a 25 percent saturated solution.

The medium was treated in the following manner: the 2-n-hexene was mixed thoroughly with the medium. Then by means of separatory funnel the medium was drawn off. The cultures were then set up in solutions of 100, 50, and 25 percent saturation. In the "saturated" solution, which is actually very dilute, hexene is quite toxic, and kills the cells; but, in a 25 percent solution of this so-called "saturated" solution very good growth was obtained. In fact, it seems to stimulate them a bit. That, of course, seems to be the case with most of these substances when we get down to concentrations that are low enough.

DR. HAYES: Dr. Hodge, would you like to open the discussion?

DR. HODGE: Are these cells sensitive to minor changes in pH, and are there enough difference in the pH of the sulphite, the acid sulphate and the other solutions to influence the growth and viability of the cells?

DR. PACE: The cells are sensitive to pH, but not too much so. It can vary a couple of units without any obvious effect. However, only in the highest concentrations of sodium bisulphite did we get a real change. In the others, we did not. We have our medium fairly well buffered, so that one wouldn't expect too great a change, except in the highest concentrations.

DR. HODGE: I was stimulated by Dr. Pace's observations that in really dilute concentration he saw stimulation rather than an inhibition of growth. I would like to know how he views this. Is this a toxic effect? Is this good? Is a little smog something that we ought to generally inhale every morning, just to stimulate us?

**DR. PACE:** This is quite a problem. I wouldn't advise people to breathe smog, without learning a little more about it. Anything becomes toxic, in high enough concentration. But there are mechanisms which may be inhibitory mechanisms themselves in nature which are balanced with mechanisms that are proceeding in the other direction. There is always the possibility of having these inhibitory mechanisms taken out of action by some substance in dilute concentrations which are not yet affecting the opposing mechanism. Finally, however, as the concentration of the substance increases, it does affect the mechanism that has to do with the opposite process.

**DR. MENEELY:** If I understood correctly, in the early part of your paper you gave some upper values. What are the lowest concentrations at which you clearly found effects from sulfur dioxide and from nitrogen dioxide?

**DR. PACE:** With nitrogen dioxide, we were actually getting growth, comparable to our so-called control cultures, at around 200 parts per million. However, with sulfur dioxide we had to get down to around 10 and 25 parts per million. These vary with the cell types. The HeLa strain seems to be very sensitive. But at least it isn't as tolerant of these concentrations as the L strain, or definitely not as much as the liver.

**DR. ESTES:** I have two questions, the first of which follows upon Dr. Hodge's question on pH. Of the amount of salt added, what about the effect of ionic strength when you are using higher salt concentrations. Certainly in the case of leucocytes we can get inhibition by increasing the ionic strength of the solution with ordinary sodium chloride.

The other question is in connection with the stimulation effect. Again referring to our leucocyte work: With very small changes in pH, I observed the same thing. A small shift in the pH of the medium will give stimulation. In that case I could relate the stimulation to a change in pH of say, three-tenths of a pH unit. In other words, the slight amount of acid was stimulatory. However, if I maintain the pH constant throughout, the stimulation disappeared.

**DR. PACE:** With our neutral salts in such low concentrations there definitely is no difference in pH, as far as we can detect. The pH will definitely have an effect. I have noted this many times on protozoan cells in work reported some years ago.

Ionic strength can be a factor when you get up into higher concentrations, but in low concentrations we obtain approximately the same results as in the control. In fact, sodium sulphite in very low concentrations may actually cause an increase in proliferation of liver cells.

**DR. FAIRCHILD:** Do you attribute the effects of these sodium salts purely to an upset in osmotic tension?

**DR. PACE:** Well, at least not at the lower concentrations. I can answer the same as I did to Dr. Estes' question. In high concentrations undoubtedly you are going to get into that problem, but not in the low concentrations reported here.

**DR. FAIRCHILD:** Even in these lower concentrations you would have an osmotic effect of these salts.

**DR. PACE:** No, because we can change the solution somewhat so that osmotic concentration is no different from the control; such as using sodium chloride in same concentration as sodium nitrite.

**DR. CAREY:** For how long was the concentration of 10 parts per million of sulfur dioxide applied in order to evoke no response?

**DR. PACE:** Dr. Thompson, my associate, may reply to that.

DR. THOMPSON: Some of the $SO_2$ exposures were definitely run for 50 days. The cultures were gassed intermittently. They received a gassing every day for the course of the study, and the cultures were thoroughly flushed out with the gas.

DR. HAYES: Then it was continued for how long?

DR. THOMPSON: Well, each culture was gassed, depending on the flow rates, anywhere from half a minute to more than a minute each time, and then this gassing procedure was repeated daily for the interval of the study. In other words, the gassing procedure simply took the place of what was normally done with a mixture of five percent carbon dioxide and air, which is a standard technique in tissue culture work.

DR. VORWALD: How long were you able to observe a single culture? For fifty days without transplant?

DR. PACE: Well, some we did, and others we had to transplant. Those that we were actually observing just to note length of time, or to carry what we would call a long-range experiment, as compared to our experiments of ten or twelve days, we would change. We kept them going in large culture flasks. It is an entirely different type of approach than that I just described.

DR. VORWALD: How long would they last?

DR. PACE: In a flask?

DR. VORWALD: Yes.

DR. PACE: Actually, I have never tested this out to the very end; but, the cultures do last quite a while, because when the cell population has increased to a point where they are dying out all that needs to be done is wash most of these weak, dying and dead cells out of the culture, put in fresh solution, and the culture is good for two or three more days. This may then be repeated.

DR. VORWALD: How do you determine the specificity of the agent which you were testing?

DR. PACE: That was by growth, noting increase or failure to increase, or actually immediate death in some cases. In some of these high concentrations when the gas or the salt was applied it was difficult to get the cells under the microscope before they were dead.

DR. HAYES: I believe that we must go on to the next paper, to be given by Dr. Mountain on the "Biochemical and Enzymatic Changes In Blood and Tissues Of Animals Exposed to Respiratory Irritants."

DR. MOUNTAIN: Those of you who attended this session last year recall that we gave a preliminary report on the effects of ozone on some of the enaymes of the lung. The first part of our paper today concerns some further details of the findings in that study.

In starting this study we made a literature search and found that very little work was available on the enzyme changes in the lungs produced by toxic agents given to animals by inhalation. The one paper that contained the most specific information was the report of Simon, Potts, and Gerard, (Journal of Biological Chemistry, Vol. 167, 303, 1947). They studied the effects of diphosgene inhalation on a number of lung enzymes, and, among the enzymes studied, the one that appeared to be the most affected by diphosgene was alkaline phosphotase. There were others which were also affected, but to a lesser degree. Since alkaline phosphatase was apparently so sensitive, it was decided to find out whether the irritant, ozone, had appreciable effects. In addition to alkaline phosphatase, we made determinations of 5-nucleotidase, which Simon, Potts, and Gerard did not cover in their study.

In the first experiment, rats weighing 200 to 400 grams were exposed under the conditions as indicated on the slide. One group was given 16.9 parts per million of ozone for one hour. Two other groups were each given 6 parts per million of ozone for four hours. We wanted to use high enough concentrations so that we would be likely to get an effect. After the exposure, lung tissue was removed from the animals and homogenized and treated according to the procedure of Reis, who has done work on phosphatase and nucleotidase content of lung. The data that we obtained are presented on the next slide in such a way that we can compare an unexposed control with the exposed animals and get the relative percentages of activity.

In order to make the data more intelligible, it might be best to look just at the relative effects. You will notice that in the high-level exposure there remained only ten percent of the control activity with respect to alkaline phosphatase. At the dose of 6 parts per million of ozone, there were two groups. One, Group A, had never been exposed to ozone before. The B group had previously been exposed to 1.7 parts per million for four hours, which according to Dr. Stokinger and others, would result in the development of tolerance to ozone. You will notice the difference between the group that had never been exposed to a low-level ozone concentration and the group which had been exposed. With the group that had not had previous exposure there was 40 percent of control activity remaining after the exposure to 6 parts per million of ozone for four hours. The "ozone-tolerant" group had 63 percent activity remaining.

In order to see what relation there was between tolerance, ozone exposure and mortality, we combined all the data from both groups and then separated them according to mortality. That is to say, we combined all the animals and classified them according to mortality. The animals that died had only 34 percent of control activity, while the animals that survived the ozone exposure and sacrificed for this purpose 24 hours after the exposure, showed close to normal activity of the alkaline phosphatase in their lungs.

The important figure in regard to nucleotidase is shown in the last row of the table. This is the "uncorrected" activity. We find that nucleotidase was also affected by exposure to ozone. Only 28 percent of control activity remained after the high exposure. However, that is much more than the residual phosphatase. Evidently nucleotidase is more resistant to change than phosphatase. In the lower-level exposures, i.e., the 6 parts per million, both groups were about the same, 81 and 82 percent of control level. Dividing the animals according to mortality, we find the group which succumbed to the exposure had 79 percent of control activity, while the group that survived the exposure had 90 percent of control activity. These results are probably not significantly different. We might say, in conclusion, that it appears that maintenance of alkaline phosphatase activity in the lung appears to be essential, certainly for survival, and that it appears to be associated with tolerance to ozone. This may be a very useful tool in appraising injury following exposure to toxic irritant agents by inhalation.

As a result of these studies, it occurred to us that it might be profitable to investigate the serum enzymes also. It seemed to us that the obvious one to investigate would be the alkaline phosphatase. We came across a very interesting finding from some work on the metabolic effects of carbon disulphide, and this encouraged us. This observation was that the magnesium-activated fraction of serum alkaline phosphatase shows a markedly increased activity following exposure of rabbits to the inhalation of carbon disulphide. It is possible that the reduction in lung alkaline phosphatase activity, described previously, might be associated with the release of the enzyme from tissue cells into the circulation. For these reasons we thought it desirable to determine if inhalation of ozone would affect serum alkaline phosphatase activity and particularly the activity of this magnesium-activated fraction.

We tried this on a single rabbit. We exposed the rabbit to 10 parts per million of ozone for one hour, a high level from the standpoint of community air pollution. The chart and the line graph show what happened. (Slide). Prior to exposure, the basic activity without magnesium was 1.25 units. With magnesium added to the substrate it went up to 1.59 units. Half an hour after exposure, the basic serum activity dropped to 1.06, while the activity with magnesium added went up to 1.80. With time, there were some further changes. The activity in the absence of magnesium dropped slightly, or perhaps wavered a bit, while with magnesium present it remained quite high, and eventually, in 24 hours, came back down to approximately the pre-exposure level. However, the basic (i.e. activity without magnesium) level here was still below the pre-exposure value.

(Slide #2) Now if you look at this line graph (a plot of the percentage increase of the magnesium-activated fraction against time elapsed, computed by taking the difference between the activity with magnesium and the basic activity values and dividing by the basic value times 100), you will notice the remarkable peak in that line which occurs within a very short time after exposure, followed by a gradual decline. (Slide #3). In the next slide this line represents the percent increase in the magnesium-activated fraction over the basic activity. It is the average of values in studies of four rabbits exposed to 10 parts per million of ozone for an hour. It shows the changes over a period of nine days. The dotted section here shows the pre-exposure percent of the magnesium-activated fraction (22-29%). Immediately after exposure we got the same pattern as we do in the single rabbit (53%). It fell back in about one day to 38%, and then we find a second rise. After a day or so, it goes up to remarkably high levels (60%), then declines, and then gradually "wobbles" back down and approaches the pre-exposure level, or drops within the range of pre-exposure values (22-26%) after four or five days.

We believe that the phenomenon is a very useful tool to study smog injury. We believe it is a useful tool for following the lung changes following inhalation exposures to toxic agents. Our studies with carbon disulphide indicate that there also we obtain this increase in activation of the serum by magnesium but, the pattern is a little bit different. We are inclined to believe, at least at this time, that the pattern we obtained here is peculiar to the lung. The pattern we get with the carbon disulphide exposure is somewhat different and may be associated with liver change.

We were, of course, interested in seeing this change, and wondered if it had practical application to studies of serum changes in people exposed to toxic agents. Apparently, it does, judging from our experience with fumigators who use a mixture of carbon tetrachloride and carbon disulphide. We found that in grain fumigators who use this material and whose absorption is probably through the skin, there is a marked increase in the magnesium-activated fraction of serum alkaline phosphatase. We were also interested in whether this would distinguish injury following exposure to various chemical agents from various disease conditions. At this time we are not sure. We may say, however, that we obtained serum for study from some patients who had lupus erythematosus, some with other skin disorders, and some with liver conditions. We found that in those diseases there is a change.

After we thought we had made quite a world-shaking discovery, we found that this phenomenon has been observed before. The first time that it had been applied to humans was published in the literature at about the time we made our observations. This is in the British Journal of Clinical Pathology, Vol 9, 333 (1956). The report notes that children in India, who are suffering from the protein deficiency disease, Kwashiokor, show the pattern of increase in the fraction of magnesium-activated serum alkaline phosphatase. It had also been observed in rats kept on a protein starvation diet for a number of years. (Rosenthal, O., et al., J. Biol. Chem. 194, 299 (1952).

From the data presented here, it may be concluded that exposure to toxic agents which act purely as lung irritants can produce changes in the serum.

DR. HAYES: I believe that this report may indicate that we have a practical test which may be used in surveys and which may distinguish between strictly normal people from those who have been exposed to toxicants. Because of time limitations, we will have to dispense with the discussion and move on to the second panel.

## PANEL I I

## THE EFFECTS OF AIR POLLUTANTS UPON MAN AND THE INTACT ANIMAL UNDER EXPERIMENTAL CONDITIONS

DR. HEIMANN: We are ready to proceed to the second panel. Dr. Hodge has agreed to chair this session.

DR. HODGE: The first presentation, by Dr. William B. Deichmann and Moreno L. Keplinger, from the University of Miami School of Medicine, is to be presented by Dr. Deichmann. His topic is, "Investigation of the Acute Effect of Nitro-Olefins Upon Experimental Animals; A Preliminary Report."

DR. DEICHMANN: I would like to re-emphasize that this is a preliminary report. We feel that it is important to report on these compounds because we think that they may play an important role in air pollution. Another point that I would like to make clear is that I am here as the spokesman of our group. The synthesis of the nitro-olefins was done in our laboratory by Drs. Thomas Mende and Kenneth Lampe. The construction of the exposure chambers was primarily in the hands of Mr. William McDonald. The actual pharmacologic studies were primarily conducted by Dr. Keplinger, while the pathology was carried out by Dr. Grady Lanier.

The compounds that we investigated are the nitro-olefins. I have put the formulas of two of these compounds on the board, namely, 2-nitro-2-butene and 2-nitro-2-nonene. The remaining compounds fall in between these two extremes. Regardless of the mode of administration of the nitro-olefins, they all elicited similar pharmacodynamic effects and signs of intoxication. For that reason I shall discuss them as a group and point out individual differences as they become apparent.

The first experiments deal with the effects of the vapors. Rats, chicks and rabbits were placed into each of two exposure chambers of approximately 30 liters capacity. The chambers were connected in such a manner that the contaminated vapors passed into chamber number 1, and from this into chamber number 2, and so on. The temperature in the chambers was essentially the same, varying between 21 and 24 degrees Centigrade. The degree of humidity varied. In chamber number 1 the relative humidity was approximately 50 percent, while in chamber number 2 it was between 90 and 95 percent. It was assumed that the concentration of a nitro-olefin was the same in both chambers. It was also assumed that oxygen and carbon dioxide tensions were not significantly different in the two chambers. In other words, variations in effect noted in the animals placed into each of these two chambers were assumed to be caused by differences in the degree of humidity only. The concentration of a given olefin in the air of a chamber was calculated from the loss in weight of the cylinder containing the olefin and the volume of air passing through the chamber. It is realized that this method is approximate and that the data require checking by chemical analysis.

Marked irritation of the eyes was the first effect noted in the animals, as indicated by the fact that the eyes were kept closed and the conjuctiva, sclera and eyelids became inflamed. Peripheral (skin) vasodilatation was evidenced by the development of redness of the external ears, nose and paws of an animal. There was marked irritation of the mucous membranes of the respiratory tract and a conspicuous increase of secretion of mucus appeared at the nose and mouth. Dyspnea became very marked during the five-hour period of exposure. All animals became cyanotic and, somewhat later, went into coma. They all died with a marked asphyxial type of convulsion. In general, rabbits and chicks were more sensitive to the vapors of these compounds than were rats. Without exception, the rabbits were the first to die.

The butene and pentene compounds caused hemorrhages in the lungs of all the animals in both chambers. There was, however, a greater volume of pleural fluid in the thoracic cavity of animals exposed at the same time to the high relative humidity. Post-mortem examination of animals exposed to the longer chain carbon compounds and to low humidity revealed no hemorrhages and practically a dry thoracic cavity. Exposure to the same compounds under conditions of high humidity induced, without exception, a thoracic cavity practically filled with serious fluid.

Acute oral toxicity studies: Both male and female rats were employed for these studies. The onset of action of 2-nitro-2-butene became apparent within five minutes, while seven to ten minutes passed before effects were noted when the other (longer chain) carbon compounds were used. With most compounds, particularly those with the lesser carbon atmos, there was a marked primary stimulation of the central nervous system, as evidenced by hyperexcitability, increased activity, tremors, and, again, clonic convulsions. There was tachycardia and reddening of the ears, nose, and paws, indicating peripheral vasodilatation, or possibly an elevated blood pressure.

As the effects progressed, the rate of respiration decreased. Dyspnea and cyanosis became marked. Subsequently, the animal developed generalized depression, decreased muscle tone and ataxia. Most of the rats suffered asphyxial convulsions and died. The survival time ranged from about thirty minutes to sixty hours, depending on the dose and upon the length of the carbon chain in the molecule. The longer the chain, the more prolonged was the period of survival.

Acute intraperitoneal toxicity studies: Rats were again employed for these studies and the signs of toxicity were very similar to those induced by oral administration; but, the onset of action, as expected, was more rapid. The central nervous system effect, particularly the clonic convulsion, was more severe. Death again was preceded by asphyxial convulsions.

Cutaneous toxicity studies: A compound was applied to the closely clipped abdominal skin of a rabbit while it was immobilized on a board. The animal was then placed under the hood in such a manner that inhalation of vapors would be negligible. After five hours of exposure the skin of some of the rabbits was washed with soap and water to remove the unabsorbed portion of the compound. No attempt was made to remove the compound from others. Difference in toxicity was not noted by these different procedures. It was felt that two factors contributed to this lack of difference, namely, 1) the compounds are rapidly absorbed through the skin and 2) they are very volatile. As a result of these two, after a period of five hours none of the nitro-olefin was left on the skin.

Immediately after topical (skin) application of a nitro-olefin, there was local irritation, pain, and erythema. After two to five hours there was local edema and discoloration, involving the whole area of application. After several days, necrosis developed with sloughing of the tissues and secretion of bloody pus. Subsequently, a hard, heavy, dark-colored scab formed over the whole area. After a period of about two months the skin healed and after about three months hair started to grow over the treated area. The signs of systemic intoxication were very similar to those mentioned previously.

Local effects on the eye of the rabbit: Application of one drop of a nitro-olefin to the eye of a rabbit caused marked local irritation of the mucous membranes and lacrimation. The blood vessels of the conjunctiva and the cornea became dilated, and the eyelid became rapidly inflamed. Somewhat later, the cornea became white, or "burned" and there was indication that the protein of the epithelial layer of the cornea was coagulated.

Effects on blood pressure and respiration: The intravenous injection of four to eight milligrams per kilogram of 2-nitro-2-hexene into an anesthetized dog caused immediate cessation of respiration lasting a few seconds. The respiration then markedly increased in both rate and amplitude. Expiration was forced. These effects lasted about five to ten minutes, depending on the dose. Simultaneous with the effects on respiration, there was a fall in blood pressure which was followed by a marked pressor effect and tachycardia, lasting from about five to fifteen minutes.

Pathology: Gross and microscopic examination of organs and tissues of animals exposed to the nitro-olefins revealed marked pathological changes. The most significant changes were noted in the lungs, such as extensive hemorrhages, edema, and emphysema. The alveoli and bronchioles were filled with edema fluid, and the cells were disrupted. The liver and kidneys were discolored, with blanched and hyperemic areas, and showed perivascular edema due to congestion and stasis. The heart showed subendocardial hemorrhages and edema in the myocardium. The mesenteric vessels were congested. There were multiple petechial hemorrhages and hyperemia in the gastoenteric tract. The non-glandular portion of the stomach was thickened and the epithelial cells were necrotic.

There were large quantities of free blood and cellular debris in the lumen of the intestines where the crypts and villi were disintegrated. The spleen showed marked congestion and loosening of reticular stroma and trabecular connective tissue. The blood was dark colored and contained many oily droplets. There was, in addition, a large quantity of a yellowish-brown to brownish-black pigment, and an abnormal concentration of polymorphonuclear leukocytes. Finally, the skin showed petechial hemorrhages, inflammation, necrosis and edema with infiltration of the treated areas with eosinophils, as is seen generally in skin burns.

In summary, we found that regardless of the mode of administration, the nitro-olefins are very toxic compounds. They produce, in addition, marked local changes in the skin or enteric tract, depending upon the mode of administration. They cause marked irritation of the entire respiratory tract, the skin and the eyes. Absorption from the respiratory or gastroenteric tract, peritoneal cavity or skin is very rapid, and signs of systemic intoxication appear promptly. These include hyperexcitability, tremors, clonic convulsions, tachycardia, increased rate and magnitude of respiration, followed by a generalized depression, ataxia, cyanosis and dyspnea. Death is by respiratory failure and is associated with asphyxial convulsions. Pathological changes were most marked in the lungs, regardless of the mode of administration.

I wrote a few figures on the blackboard to give you an idea of the general order of toxicity of these compounds. In the rat, for instance, when the nitro-olefin is given intraperitoneally, the toxic dose ranged from 0.08 to 0.28 grams per kilo. As the carbon chain increased the compounds became less toxic. When given to the rat orally, the lethal range was 0.28 to 2.1 grams per kilo. Concentrations in the air of approximately 200 to 500 parts per million, based on vapor, killed rabbits in about two to three hours. Less than 50 parts per million per dose produced no systemic effect in rabbits.

Finally, we carried out a few tests on eye irritation in man using 2-nitro-2-butene. We found that 3.3 parts per million produced eye irritation in man in approximately 2 seconds; 2.2 parts per million produced irritation in approximately 21 seconds; and, 0.2 parts per million produced eye irritation in approximately 2 minutes.

DR. HAYES: These are very striking effects. I wonder if some of us, who are not connected directly with air pollution, could be informed about the occurrence of these materials in community air. What concentrations have been found in air?

**DR. DEICHMANN:** I wish I could answer your question, Dr. Hayes. I believe that Dr. Chambers may be able to reply.

**DR. CHAMBERS:** I wish I were in a position to answer the question directly. We can say this: There is experimental evidence in the literature, and certainly a great deal of theoretical evidence as well, that compounds of this type must occur in a reaction between olefins and nitrogen dioxide, as they come from the auto exhaust or other sources. There are also other routes, for example, through oxidative action by ozone which, in theory, would produce them. They have been produced and demonstrated in systems such as those mentioned at much higher concentrations than any of the reactants occur in the smog or in the atmosphere that we have observed.

You will notice that the eye irritation in man reported by Dr. Deichmann occurred with exposures of the order of a few parts per hundred millions, and they occurred within a couple of minutes in man at this extra-ordinarily low level. We have confirmed this on material supplied to us by Dr. Deichmann, and also other materials which we have synthesized ourselves. We found effective concentrations in the order of somewhere between 10 and 15 parts per billion.

There is, however, a difficulty in handling these materials, as Dr. Deichmann indicated. This is true particularly at these low concentrations. They are readily absorbed by any surface with which they come in contact, and have a strong tendency to polymerize under atmospheric conditions. This, of itself is of interest in connection with other phenomena in connection with the smog process.

We thought we might be able to find these compounds in smog by reason of the fact that such a structure contains a conjugated double bond, and, therefore, might show some specificity of absorption in the ultraviolet range. We have checked this out in a 25 meter ultraviolet cell, and find there is absorption in that region, but it is not sharp. It is diffuse. And, unfortunately, it is in a region in which many other things in the atmosphere also absorb. As far as infrared identification is concerned, even with the 500 meter cell, concentrations of the order of a few parts per billion are well out of reach of any optical procedures.

We have one other line which is more or less indirect. As mentioned earlier the soluble fraction of the atmospheric aerosols during smog shows a polarographic half-wave potential somewhere around 1 to 1.1 volt. It is an interesting fact that the nitro-olefins, e.g., 2-nitro-2-butene and 2-nitro-2-hexene, show the same half-wave potential. We are investigating the possibility that a polarographic method applied to the particulate collection from the atmosphere will provide a demonstration of the presence of this type of structure in the smog.

There is one other thing I would like to add. We have found that in addition to eye irritation these substances, at very low concentrations, produce plant damage. We haven't reduced this to a quantitative base yet, but the qualitative damage is of the "smog" type and is produced at very low levels of concentration.

I agree that the big problem now is to demonstrate a relationship between the laboratory observations that have been made on eye irritation and toxicity with an actual occurrence in the atmosphere. There is no direct establishment of that relationship yet.

MR. KRACKOW: At the outset I would like to mention that this appears to me to be a very commendable effort, one in which the chemist, the pharmacologist and the toxicologist work so closely together. Possibly you also had engineering talents on this effort.

Dr. Deichmann, you realize the possible error associated with the lack of measuring concentrations by analytical methods.

These types of materials are highly adsorptive on surfaces; for example, the walls of your chambers and the fur of the animal. Have you done anything to characterize the atmosphere, analytically? This may well be an error of omission that will completely prevent any attempt to correlate toxicological properties with chemical structure, one of the basic things that you are trying to arrive at in this study.

During World War II the Chemical Warfare Services, in both this Country and in Britain, worked on these types of materials. Unfortunately, some of this information is still classified. In these studies, up to a point, one did see a certain amount of correlation of toxicity with structure. Would you try to help us in seeing whether you have anything along these lines, other than the fact that the longer carbon chain compound seems to indicate less activity? Do you have anything else or anything more closely akin to this correlation of structure and toxicity?

Why do you use the five-hour period before decontamination, in your skin studies? Was there a firm basis for this, or was this time chosen arbitrarily?

In the intravenous studies in the dog, you mentioned the use of anesthesia. Do you think the anesthetic in any way modified some of the pharmacological findings which you saw? Would studies of this type, done without the anesthesia, have given you a different picture? What was the anesthetic?

Have you seen anything that might suggest methemoglobinemia? Did you determine methemoglobin levels in the blood of the animals?

In your studies of man, is the irritation the type of effect that we would normally associate with lacrimation, such as occurs with tear gas? Is this the type of irritation you mean?

DR. DEICHMANN: As mentioned earlier, this report is very preliminary. On the whole, I have to reply in the negative to most of your questions. If I could have had my way, I would not have reported anything today.

I am fully aware of the lack of accuracy, based on the absence of analytical data, and this is the reason why I would not have presented a report at this time. The $NO_2$ group, of course, plays an important role in the toxicity of the compound. The length of the carbon chain probably is of secondary importance, since it appears that the toxicity decreases with an increase in carbon atoms. Whether these speculations are entirely correct, only future studies will have to show. Again, I would like to re-emphasize that the work done and presented here is of a very preliminary nature.

Generally, we are using five hours of exposure, for inhalation and for skin exposures. We are doing this because I have done this for years with other compounds. I have exposed animals for five hours which is less than people are generally exposed to in industry. But I like five hour periods of exposure, because it usually gives the analytical people, and also those who might carry out blood and other studies, sufficient time to complete their tests on the same day that the animals were exposed.

We used sodium pentothal as an anesthetic. No matter what anesthetic one uses, the results will be influenced.

I am skeptical about methemoglobin. I would never say that if the blood looks brown that we are dealing with methemoglobin. I would like to check this. This we have not done.

The eye irritation studies were done on medical students and members of our faculty and staff. For this purpose we built an exposure chamber which has the approximate proportions of a coffin. It has a capacity of 500 liters.

We have attached at one end a skin diver's mask. It was glued to the cage. An experimental subject would simply extend part of his face into the mask and thereby expose both eyes and nose. We clamped the nose. In front of the eyes was a shutter. As soon as the individual was ready for the exposure, we opened the shutter, and whatever vapors were in the exposure chamber had a chance to come in contact with the eyes almost immediately. What we measured was the time interval between opening of the shutter and onset of irritation.

DR. ZAPP: I think that interest in the toxicology of the nitro-olefins centers on the fact that here we have a powerful irritant which could produce eye irritation at concentrations which might reasonably be expected in smog. Furthermore, there is at least some theoretical evidence that this kind of material could be present.

I may say, also, that the dichloro-butenes are the same kind of material in that they too are powerful irritants and vesicants. It may be that in a smog mixture we are not only dealing with nitro-compounds, but, under certain conditions, we might run into halogenated olefins, which could produce this same kind of effect.

DR. HODGE: Would you comment on this, Dr. Deichmann?

DR. DEICHMANN: Dr. Zapp may be correct, but I would like to see quantitative comparisons.

DR. CHAMBERS: I would like to comment on that point.

It has been demonstrated that the production of eye irritant in irradiated smog constituents is a function of the amount of $NO_2$ present. When $NO_2$ is omitted, you get very little, if any, irritation. I have concluded that we are not dealing with chlorides because chlorine is present in the air in almost all circumstances.

DR. HODGE: I would like to give the privilege of the floor for a question or two.

DR. FREDRICK: For many years, we have been studying exhaust gas in enclosed spaces. We have never been able to correlate irritating effects with aldehydes or the usual things irritation is ascribed to. It has been clear to us for some time that there is some other parameter involved. This may well be the explanation for it.

DR. GOLDSMITH: I want to commend Dr. Deichmann for this very impressive job, and to ask the question as to whether or not enough of the chemistry of these compounds is known so that one could say, for instance, what some of the hydrolysis products of these substances would be.

DR. DEICHMANN: I think the chemists here are in a better position than I to answer this question.

DR. CATCOTT: Dr. Deichmann, you said something about the relative susceptibility of chicks when compared with the other laboratory animals which were used. Would you mind repeating that?

DR. DEICHMANN: Dr. Keplinger, will you please answer this question?

DR. KEPLINGER: Chicks elicited signs of intoxication quite rapidly. They threw back their heads; they gasped; and they were obviously suffering effects of irritation. This was noted before the rats showed any signs at all. Dr. Deichmann made the point that even though the chicks started showing the signs sooner, their survival time was comparable to that of the rats.

DR. CATCOTT: What about the microscopic changes?

DR. KEPLINGER: The pathology in the chicks has been similar to that of the other animals. There was a lot of damage, particularly in the liver and the lungs, the air sacs were particularly filled with edema fluid in the exposures involving high relative humidity.

DR. HODGE: I am afraid we will have to stop this discussion at this time.

The second paper this morning, by Dr. Heinrich Brieger of the Jefferson Medical College of Philadelphia, is entitled "Ingestion As A Factor In Inhalation Experiments; A Preliminary Report."

DR. BRIEGER: May I point out that the work reported herein was executed by Charles W. LaBelle and his assistants.

When this project was suggested by me, little was known of the significance of gastrointestinal deposition in so-called "inhalation exposure." Recently, intestinal deposition of "inhaled" radioactive particulates has been investigated, and its importance for estimating total body burden demonstrated.

This paper deals with a systematic study of the mechanisms and the role of intestinal deposition following inhalation or intratracheal injection of particulates. The material used primarily was D and C Green, an insoluble and inert dye. Rats were exposed to 20 mg./cu. m. of 6- or 2- micron particles of the dye for seven hours. The tissues were analyzed at intervals up to two weeks following the exposure.

The patterns seen following exposure to 6- and 2-micron particles, respectively, were qualitatively alike. The chief sites of primary deposition were the skin, the gastrointestinal tract, and the respiratory organs. At each site, the quantity of dye found increased during the exposure, but in a non-linear fashion. In both studies, it was possible to identify three characteristic phases in the re-distribution process. During the exposure and for a short time thereafter, the largest amount of material was found on the skin. For this period, the deposits in the gastrointestinal tract were intermediate, and the deposits in the lungs were the smallest. Most of the large deposit on the skin, however, was held only mechanically and was rapidly removed after the animal was no longer exposed.

At the end of about 24 hours, a new phase made its appearance, with the amount of dye in the gastrointestinal tract being larger than in any other part of the body. In the animals examined at 24 hours, the gastrointestinal tract contained 52 and 56 percent, respectively, of the total body burden, even after an amount substantially equal to the total body burden at 24 hours had passed through the intestines and had been eliminated in the feces. While this second phase is necessarily transitory in character, it may persist for several days, during which time a very large gastrointestinal dose may be built up. Within two weeks, the concentration of the dye in the gastrointestinal tract fell to low values. A third phase, which is relatively permanent, had ensued. After seven to fourteen days following exposure, the lungs had retained a much larger proportion of the original dose than any other organ, with the result that eventually the lung burden was the highest. Essentially, the same pattern was observed following exposure to activated uranium particles.

Following inhalation of 6-micron particles, approximately 41 percent of the total lung dose was expelled from the lungs during the first 24 hours. It was strongly suspected that this part of the lung burden had been transferred from the lungs to the gastrointestinal tract. However, it was impossible to demonstrate this directly in an inhalation experiment because of the large amounts of dye already present in the intestines. Hence, the dye was given by intratracheal injection. In a series of eight rats given comparable doses of the dye by intratracheal injection, an average of 23 percent of the injected lung dose was recovered in the feces. This accumulation of the dye in the intestinal tract can only represent transfer from the lungs.

Wide variations seemed to be associated with rather small differences between experiments. The importance of particle size became especially evident in the third phase of the experiments since the clearance of particulates from the lungs was significantly altered by changes in particle size. Reduction of the mean particle size from 6 micra to 2 micra resulted in a six-fold increase in the half-life of the material deposited in the lungs, with the initial lung burden (on a weight basis) being the same in the two experiments. It had also been found in this laboratory that changes in the lung burden cause a similar effect since the percentage of the dose cleared from the lungs within 24 hours was increased from 10 percent to 90 percent by the addition of inert dusts. There was also some evidence suggesting that differences in the rate of pulmonary clearance can be ascribed to differences in various physical and chemical properties of the particulates used.

Radiologists are aware of the importance of the initial skin deposition and have given recognition to the role of the intestinal burden; the maximum permissible doses for inhalation exposures of certain isotopes, such as Thorium-234, Radium-223, and Polonium-210, were calculated on the basis of the doses received by the gastrointestinal tract. However, the observation that inhalation of particulates is, temporarily , followed by heavy intestinal deposition is of much more general significance. The specific patterns of dissolution, metabolism, and absorption in the gastrointestinal tract may produce a type of systemic intoxication different from that produced by pulmonary deposition.

That inhaled particulates can move from the lungs to the esophagus is known. The experimental results presented show the magnitude and the pattern of this redistribution process and some of the factors on which it depends.

DR. HODGE: Dr. Zapp, will you open the discussion?

DR. ZAPP: Dr. Brieger, I must confess to being a little bit surprised by the magnitude of the gastrointestinal burden in the early stages, and I wonder what contribution, if any, might be made here by the licking of the fur. While I recognize that other transport mechanisms exist, is it complicated here by the "licking factor," or did you take precautions to prevent that?

DR. BRIEGER: That was exactly the first question I expected. I have run a set of experiments with animals -- rabbits in this case -- preventing them from licking, and I obtained some differences. But more important than this is the fact that following intratracheal injection 23 percent of the injected lung dose appeared in the gastrointestinal tract and was recovered in the feces, and licking obviously could not have played any role.

DR. ZAPP: Do you have any idea how this curve might have been modified quantitatively, if there had not been licking?

DR. BRIEGER: In the inhalation experiments?

DR. ZAPP: Yes, in the inhalation experiments.

DR. BRIEGER: Yes, I have some figures on rabbits but, unfortunately, I don't have them here. Licking undoubtedly increases the intestinal burden but not as much as one would expect. There is another point, Dr. Zapp. The skin burden disappears rapidly, and yet the intestinal burden increases, while the skin is practically free of the dye, or the radioactive material, or whatever else we have used.

DR. ZAPP: I have just one more brief question. Maybe Mr. Krackow can answer this. There have been many human experiments on inhalation of harmless aerosols, dyes, fluorescent dyes, and things of that sort. Has any study been made of the fecal excretion of these particulates after man exposures?

DR. BRIEGER: With some radioactive material. However, no systematic studies have been done.

DR. HODGE: Mr. Krackow?

MR. KRACKOW: I think Dr. Brieger's presentation represents so many facets of a very complicated problem that I question whether we could possibly, in the time allotted, go into all of the ramifications of this type of a study.

We have always been interested in the components of oral toxicity that one gets in an inhalation of particulates. I think it is very difficult to criticize any features of this study. We see a lot of elements in here that make us wonder, particularly the skin-loading aspect of this problem. I am not too sure whether we can attribute a blow-off as the major factor in the removal of the skin deposition feature. The implication is that there is a considerable amount of skin absorption of the material deposited on the skin. Is this what the author is attempting to demonstrate here?

DR. BRIEGER: Of course, we cannot demonstrate it here, because the dye is not absorbed. The implication is that absorption, or penetration, speaking of radioactive material, is a most important factor. Looking at the magnitude of the skin load, one should expect quite marked effects of penetrating materials, and so far I agree with you entirely. But these experiments do not demonstrate it.

MR. KRACKOW: Are the skins clipped?

DR. BRIEGER: No.

**MR. KRACKOW:** It might be of interest to the group to cite just very briefly one or two experiments we have performed. We were concerned with correlating the effect of particle size on the distribution of what gets into the lung and what gets into the gastroenteric tract, and one always has the difficulty of making truly homogeneous aerosols. We hit upon a system of making glass spheres of truly 2-micron particles, 5-micron particles, 1-micron particles, and sub-micron particles. Exposing rabbits, hamsters, rats, and guinea pigs to these various sizes of glass spheres, by inhalation, we generally found 15 to 30 percent of the inhaled spheres deposited in the gastric tract.

**DR. HAYES:** I believe Dr. Brieger's experiments were not designed to test the transport of material which did in fact get into the alveolar spaces in contrast with material which happened to fall out somewhere before that. Obviously -- or at least I think it is obvious -- that sort of thing is one of the reasons why the larger particles were more efficiently mobilized from the lungs, and the smaller particles were less efficiently mobilized.

Some remark was made about phagocytosis. I would like to ask the speaker, or perhaps someone else, who would like to speak to the question, what experimental evidence do we have on the mobilization of material from the alveolar spaces, in contrast with just the respiratory tract in general?

**DR. BRIEGER:** There is quite a bit of literature on stimulation of phagocytic action. However, when you go into this matter very carefully, you find little evidence of such stimulation. We have tried to supply this evidence, and we are still working on it. What I have seen so far, guided by my pathologist, is not as striking an increase in phagocytosis as I had expected. But I don't want to say that this is our last opinion. We are just trying to establish a numerical estimate of the increase in phagocytosis. I also have in mind to evaluate ciliary action by causing ciliary paralysis, or partial paralysis. Your question is very pertinent. There is plenty of literature, but very little evidence.

**DR. HODGE:** We have time for perhaps one or two questions from the floor.

**DR. WRIGHT:** I would not like to leave here without having clear in my mind whether there has been demonstrated a pathway for particulate material from the lung to the intestinal tract with regurgitation first up the trachea, and then being swallowed. Do you infer that you have demonstrated a pathway from lung to intestinal tract without first coming back up the trachea for particulate material?

**DR. HODGE:** May I repeat the question, Dr. Brieger? Do you assume all of the transport into the G. I. tract from the lung has occurred by motion of the particles up the trachea, and into the esophagus?

**DR. BRIEGER:** Yes, I do. I have enough evidence to be convinced that this is really transport from the lung to the upper respiratory tract into the gastrointestinal tract. Regurgitation may take place occasionally immediately following intratracheal injection but not in the later phases.

**DR. HODGE:** We will proceed to our next paper of the morning by Dr. Earl J. Catcott, from the Department of Public Health, in the State of California. This paper is entitled, "Veterinary Research in Air Pollution."

**DR. CATCOTT:** During the past year, several investigations have been conducted in Los Angeles County, California, to determine whether or not animals are injured by air pollution. This research has been stimulated chiefly by the interest in searching among animals for a biological index of air pollution injury. Additional impetus for veterinary research developed from reports that laboratory animals suffered pathology as a consequence of their exposure to chemical components of smog and also to synthesized smogs. Specific interest in the effects of air pollution present in Los Angeles County developed from observations by poultrymen that chickens failed to grow and produce there as in other areas of the State and that avian morbidity and mortality rates were higher in this section of California.

A survey of 309 veterinarians located in Los Angeles and Orange Counties disclosed that definite associations between ambient polluted air and animal diseases have been difficult to demonstrate. However, one-third of 135 veterinarians who responded to a questionnaire concerning this subject observed that dogs exhibited signs of ocular and upper respiratory tract irritation during intervals of dense smog. This survey has been complemented by similar observations made by breeders of dogs. In contrast, the great majority of the breeders and caretakers of pet birds have not observed alterations in behavior or health in this species which could be associated with air pollution.

The available necropsy records of poultry and other domestic animals have been examined. With the exception of poultry, the records concerning animal mortality in Los Angeles County are few and quite incomplete. It has not been possible to correlate animal mortality with the occurrence of air pollution on the basis of this data.

Both egg and milk production data for animals located in Los Angeles County have been examined. These statistics have been collected on a monthly basis. Neither monthly fluctuations of any significance were found in this data nor were there appreciable differences in the productivity of animal groups located within and outside the "smog" area.

On the basis of these experiences it appeared that the most fruitful epidemiological studies of air pollution and animal health would be prospective rather than retrospective investigations. Accordingly, a pathological survey of dogs located in Los Angeles County has been conducted and a field experiment involving chickens was completed during the past year.

## A Survey of Pulmonary Pathology in Dogs

Two groups of dogs were selected from locations in Los Angeles County which have been observed to experience contrasting degrees of air pollution. Twenty-three dogs were obtained at the Pasadena Humane Society which is located in an area of relatively dense air pollution. Six dogs came from a veterinary hospital located near the Pasadena Humane Society. Twenty-two dogs were obtained from the West Los Angeles Animal Shelter which is located in an area of relatively light air pollution. The subjects were selected for study on the basis of their being identifiable by age and period of residence in either Pasadena or West Los Angeles. These animals had been submitted to the respective animal shelters by their owners with the request that euthanasia be performed.

The age range of the 51 subjects was 4 months to 18 years. The mean age was a fraction over 6 years. All of the dogs were ambulatory, reasonably active and apparently free of acute illnesses. Their euthanasia was accomplished by rapid decompression. In all instances the necropsy was done within two hours following death. The respiratory tracts were removed in toto. Tissue specimens were obtained from five areas of each respiratory tract, including the trachea, main bronchi, terminal bronchioles and pulmonary parenchyma. Neither the tracheas nor bronchi contained gross evidence of pathology. Pulmonary neoplasia, cysts, and abscesses were especially sought, but not found.

No pathognomonic pattern of morphological changes could be observed either in the tracheobronchial epithelium, the subepithelial glands, or the pulmonary parenchyma. Sections taken from the fifty-one dogs were compared with sections from similar sites taken from dogs exposed to artificial smog as part of an earlier research effort on the effect of synthetic smog on the pulmonary physiology of dogs. The changes previously produced in experimental animals and sought in the current group included increased secretion of mucus, focal areas of epithelial denudation, marked peribronchial and peribronchiolar cellular infiltration, and focal areas of an entity arbitrarily designated as smog pneumonitis. Changes observed in the experimental dogs could not be identified in the dogs under current study.

## Observations of Chicks Raised In Two Different Areas of Air Pollution

Two groups of cockerel chickens were raised in sunshine brooders at locations in Arcadia and Ontario, California. Arcadia is located in a region of relatively dense pollution while Ontario's exposure has been relatively light. The severity of air pollution during the experiment was measured by the degree of typical damage occurring in plants placed beside each of the brooders. The interpretation of plant damage due to air pollution represents the only measurement of this environmental influence. Minimum and maximum temperatures were recorded daily at each location.

The original number of birds in each flock was 102. These chicks were selected from a single brood of a genetically-related strain of Leghorn chickens. They were observed for an interval of three months starting on July 18 and ending on October 8, 1957. Two chicks from each flock were killed each week with pentobarbital sodium given intravenously and examined at necropsy. Additional birds were sacrificed on three occasions during the experiment to supplement the macroscopic observations. Body weights were recorded of all the chicks which were necropsied. During the necropsies the appearance of the abdominal and thoracic viscera was observed and abnormal areas were described. Portions of the trachea, syrinx and bronchi, and pulmonary parenchyma were selected for microscopic study.

The two flocks remained healthy during the experiment. Their growth rate, vigor and appearance were considered within normal limits for Leghorn chickens raised in accordance with good management and care. At the termination of three months 42 chickens remained in each group. The great majority of the 60 birds removed from both flocks were those which had been deliberately sacrificed for observation at necropsy. A few birds in each flock were lost due to cannibalism.

A difference existed in the body weights of the chicks which were sacrificed each week. The total weight of the 18 chicks sacrified from the Ontario flock was 31 pounds. The total weight of the 18 chicks sacrificed from the Arcadia flock was 33 pounds. Additional weight comparisons were obtained at the termination of the experiment when the 40 chicks remaining in each flock were weighed. The Arcadia group weighed 121 pounds and the Ontario birds weighed 114 pounds. While the chicks which were sacrificed weekly were selected at random, those from Arcadia were heavier than the pair from Ontario except on the eleventh week. It was not possible to attribute the difference in weight gains experienced by the two flocks to variances in feeding practices or differences in exposure to pathogenic organisms. The greater heat to which the Ontario flock was exposed most likely accounted for this weight difference.

The major organs of the abdominal and thoracic cavities of the sacrificed chicks appeared normal until the seventh week. From the seventh week until the termination of the experiment, 15 chicks were necropsied whose livers and/or kidneys were discolored and friable in consistency. Petechiae were observed within these lesions in four chicks. Nine of the birds in whom the described lesions were found came from the Arcadia flock and six from Ontario. Investigation of the cause for this pathology has resulted in the tentative conclusion that it occurred as a consequence of holding the chicks in poorly ventilated boxes prior to their necropsies.

The tracheal and bronchial tissues were examined microscopically by comparing each slide on the basis of the following criteria: 1) numerous goblet cells; 2) pale cytoplasm; 3) pale, large nuclei; 4) cilia absent or flattened; and 5) blood vessels distended. The pulmonary tissues were compared on the basis of: 1)bronchiolar lymph follicles enlarged; 2) lymphocytic infiltration around alveoli; 3) numerous erythrocytes both within and outside the alveolar capillaries, and 4) presence of fluid in the alveoli.

There were 90 observations of the described morphological variations in the tissues obtained from the Ontario flock and 88 similar observations in the tissues from the Arcadia chicks. There were no significant differences between the numbers of any single morphological variation observed for the two groups of chicks. It was impossible to correlate the degree of exposure to air pollution with any of the morphological variations found in the tissues.

Two characteristics of the pulmonary tissues, perialveolar infiltration with lymphocytes and increased numbers of erythrocytes, were observed in progressively increasing numbers as the chicks became older. This stimulates the speculation that these morphological variants developed more frequently as the time of exposure to exogenous influences became longer. It is of interest to note that these were the most striking changes observed in two chicks experimentally exposed to ozone. It is impossible to incriminate air pollutants, or any other exogenous influence, as the cause for these morphological variations on the basis of this experiment.

Plant damage characteristic of that caused by Los Angeles smog occurred on 49 days at Arcadia and 25 days at Ontario. These numbers represent 59 and 30 percent of the 83 days of the experiment. The days of plant damage were well distributed throughout the experiment with one notable exception. Plant damage due to smog did not occur at Ontario during the last week of the experiment.

The maximum daily temperatures which were recorded at the test sites varied appreciably. The average maximum daily temperature at Ontario was 99.5° F. during the 83 days of the experiment. This was 8.5° F. higher than the average maximum daily temperature at Arcadia. The highest temperatures were recorded during September and the most extended periods of temperatures over 100° F. occurred during this month. It was during September that the majority of the macroscopic lesions were observed at necropsy.

There appeared to be greater association of the macroscopic pathology with high temperatures than with other environmental influences. There was no apparent correlation between the histological observations and high temperature.

## CONCLUSIONS

After summarizing this past year's experiences it appears that more elaborate techniques must be employed to detect the minute and long-term effects of air pollution on animals. Experiments which are designed to demonstrate alterations in function may prove more fruitful than those which are directed exclusively at discovering morphological variations. At the present time, a new experiment involving chickens is being developed. This investigation is scheduled to extend over a longer period during which measurements of egg production, fertility rate following artificial insemination, and hatchability of fertilized eggs will complement observations of morbidity, mortality and morphological changes.

DR. HODGE: Mr. Krackow, would you like to comment?

MR. KRACKOW: Dr. Catcott's report has a resemblance to the type of finding we see in some of the studies on humans. His results are essentially negative, in that there is no demonstration of adverse effects on the health of the animals when exposed to a smog situation. Some day we may be able to find enough data to make some sort of a correlation.

DR. HAYES: It certainly is true that the experimental results were of a negative sort. There is one thing I would like to get clear, however. In the last sentence of the first paragraph of the mimeographed abstract Dr. Catcott states that poultrymen allege that chickens fail to grow and produce about Los Angeles as they do in other areas, and that avian mortality and morbidity rates are higher. Did you have any way of assessing that? Do you have any real measurements to indicate whether what the poultrymen say is true?

DR. CATCOTT: The Kimber Farms poultry organization has a fairly elaborate statistical section. This was the group that initiated the reports that a particular commercial strain was not performing in one area of California as it did in others. They have some rather elaborate statistical data concerning the performance of chicks for periods of ten weeks, and also in reference to mortality and morbidity, as well as a record of productivity after they came into their egg-laying period. Finally, they have mortality records for the chicks up to a period of one year. The data which they originally presented to us indicated that in the areas of California in which air pollution is recognized to a measurable degree, chicks did not produce as well, nor did they survive as well, as chicks living outside of the so-called smog areas.

DR. HAYES: Did they take into account variations in ambient temperature, feed, and other things that might affect these chickens?

DR. CATCOTT: I doubt it.

DR. CHAMBERS: I must point out that when these chick data were first brought in from the distributors in question (Kimber Farms) there was no identification of the geographical locality of the particular farms that were allegedly suffering. There were several dozens of such farms. Simply on the basis of the reported deficiences of egg-laying performance and in mortality, we grouped the farms by geographic distribution and we discovered that in all but a very few cases they fell into two groups, clearly distinguished by proximity to or remoteness from an urban area, such as Los Angeles or San Francisco.

That was the first hint we had that there was anything to this. Whether that is related to air pollution or to something else, I do not know. I think, however, it would tend to eliminate the temperature factor because the temperature situations are quite different in the bay area as contrasted with that of the Los Angeles area.

DR. MENEELY: Dr. Hodge, I would like to make a comment.

The statement has been made that when your life is shortened, the shortening may be "at the end" or it may be "out of the middle." There is evidence that the aging process in man progresses at different rates in different parts of the world. Some of you doubtless are familiar with the studies of Swedish women that have been drawing a lot of attention recently.

It would appear that when something happens which is diffusely adverse it shortens life out of the middle rather than chopping years off the end. In other words, the same degenerative processes that occur in everyone, come on earlier. In animal studies one may find the same thing early in two populations which might really ultimately be quite different as to their survival.

With regard to evidence from the veterinary field, we are confronted with a problem that there is a dea low-ebb of interest in "pastoral geriatrics." Longevity is something to be deplored in farm animals, with the exception of certain celebrated race horses whose functions now are largely ornamental, even though they were preserved after their racing day, possibly for other reasons. The fact of the matter is that we know very little about longevity in animal species. We need to guard very carefully against misinterpretations because of that fact. If a fairy waves a wand over one population, and says it shall live 20 percent longer than another population, it will still die of the same diseases; but, at a somewhat different time.

DR. ZAPP: I think this report points up the tremendous difficulty of comparison between two groups on an epidemiological basis because of the virtual impossibility of assuring that there is equality in all other things, except the single environmental variable under study.

I would like to make another comment. This is a report of a test under actually prevailing smog conditions. When we examine the nature of the injuries that have been attributed to smog, I think they fall into two types, eye irritation and irritation of the respiratory tract. In those cases of very severe smog exposures, such as occurred in Donora, the Meuse Valley, and London, there were actual increases in mortality rates which were attributable to the smog. These, however, were mainly in those persons who were already suffering from pre-existing disabilities. So, it is mainly in this class of person that one would detect toxic effects of the smog rather than in the normal healthy group.

It would seem, therefore, that if the dog, the chick, or whatever experimental population we are studying, does not happen to be burdened by the degenerative disease, it is quite likely one would not detect any specific pathological changes attributable to the smog itself.

DR. HODGE: The next paper on the program this morning will be by Dr. H. E. Stokinger, Mr. W. D. Wagner, and Olga J. Dobrogorski from the Occupational Health Field Headquarters, here in Cincinnati. This paper will be presented by Dr. Stokinger. It is entitled, "The Effect Of Respiratory Irritants As Modified By Oil Mist Aerosols."

DR. STOKINGER: We thought we had a number of good reasons for the performance of this study, of the combined effects on animals of oil mists and respiratory tract irritants.

One of the obvious ones was the fact that there is a significant proportion of oil mist of one sort or another in urban smog areas. The second reason is that as far as I can recall there has never been a study made of oil mists that are well defined as such, and where a gas also is characterized. The third reason is a little more of a personal one. This arose in the following way: Shortly after we announced that ozone was a fairly toxic gas and lowered the threshold limit for daily exposures of workers from one to one-tenth of a part per million, we began to be badgered by people, asking, "How does this come about, since, if ozone is so very toxic, why is there not some effect observed in places like Los Angeles where, at least, on past occasions there have been ambient air levels of five-tenths of a part per million or more?"

As we did our work we came up with at least a part of the answer, we thought. This was that the "tolerance" factor that you heard about this morning -- ozone, it seems, is essentially its own antidote against the development of acute effects. We should have stopped there, perhaps, and called the problem "solved." We have continued, however, and recently we observed that ozone indeed produces an insidious chronic effect if inhaled at fairly low levels for a continued period, say, for a year or so. We demonstrated chronic irreversible changes in the lung characterized by fibrosis in small animals exposed to one part per million for a year. Something here appeared to be inconsistent.

The next thought was: Is there a component in the atmosphere that can ameliorate the toxicity of ozone -- assuming, of course, that the analytic values are really true and that they have been determined to be ozone and not something else?

It seemed to us that we should perhaps determine whether an oil component possibly could be the factor that would suppress this acute and the highly insidious form of toxicity of ozone. For this we used mists of typical oils. One of them was a standard one of mineral oil, and the other was motor oil. The experimental design was very simple. It consisted mainly of utilizing the facts we already had well established in regard to the LC-50 dose of ozone in experimental animals.

So you can see that in administering oils with these lethal concentrations of ozone, any departures from this effect would be attributable to the oils. So we proceeded along those lines and did short-term, four-hour exposures at lethal ozone concentrations. Of course, we had to investigate the particle size of the mineral oil, produced by rare oil nebulizer. We determined the particle size of this mist at the operating conditions used to be 0.87 micron by the cascade impactor method. Then we checked this by a specially designed electrostatic precipitator. Motor oil under the same conditions of nebulizing had a one-micron mass median particle size, and the standard-geometric deviation was around 1.6. (This was an SAE-15 oil.) The concentrations were analytically determined. We determined the oil mist concentration by an electrostatic precipitator which showed a 99.6 percent efficiency.

The ozone concentration was determined, even in the presence of the oils, with a high degree of accuracy, because we found that in using concentrations of four parts per million there was only 7 percent reduction of ozone. These oils are, therefore, highly saturated cycloparaffins, as well as they can be characterized.

The next thing was: To investigate the solubility of the ozone in the oils. If there were appreciable physical solubility of ozone in oils, there would be a considerable difference in the amount of ozone that is brought into the lungs. We found there was no measurable ozone solubility in either of the oils. This was a surprise to us, because we had been led to believe from the technical literature that ozone might have an appreciable solubility in these oils. By our method, which detects, but does not quantiatively determine, 0.05 parts per million, we could not find any detectable amount of ozone in two and a half cubic centimeters of oil. This immediately eliminates the factor of the physical effect of the oil bringing the ozone down in the lungs and modifying the response.

From the first slide (Table 1) you can see that when we used oil mist and ozone simultaneously there was no reduction of effect. If anything there was a slightly enhanced response.

Table 1.

EFFECT OF MINERAL OIL ON 4-HOUR $LC_{50}$ OZONE IN RODENTS
OIL MIST CONCENTRATION 400 $mg/m^3$

| Animal Species | $O_3$ Concentration, ppm Av. | Range | CT ppm-hrs. | MORTALITY Number | Percent |
|---|---|---|---|---|---|
| | | Simultaneous Mist and $O_3$ | | | |
| MOUSE | 4.3 | 2.6-5.4 | 17.6 | 41/55 | 75% |
| MOUSE | 4.3 | CONTROLS | 17.6 | 14/20 | 70% |
| MOUSE | - | CONTROLS | - | 0/20 | 0% |
| RAT | 4.1 | 2.8-4.8 | 16.0 | 16/16 | 100% |
| RAT | 4.1 | CONTROLS | 16.0 | 8/8 | 100% |
| RAT | - | CONTROLS | - | 0/8 | 0% |
| | | Oil Mist Followed Directly by $O_3$ | | | |
| MOUSE | 4.0 | 2.6-5.0 | 16.1 | 14/80 | 18% |
| MOUSE | 4.0 | CONTROLS | 16.1 | 5/10 | 50% |
| | | Oil Mist Followed in 18 Hours by $O_3$ | | | |
| MOUSE | 4.3 | 3.9-5.0 | 16.2 | 19/60 | 32% |
| MOUSE | 4.3 | CONTROLS | 16.2 | 5/10 | 50% |

I should have mentioned that exposure to the oil was at 400 milligrams per cubic meter. That was chosen on a molecular weight basis of the oil of ten times the ozone concentration. Ozone expressed as milligrams per cubic meter is slightly over eight, and assuming an average molecular weight for oil mist, 400 $mg/m^3$ represents ten times the ozone concentration. This concentration of oil mist cannot be seen; it may seem to be a large concentration, but it is not visible in an 18-inch diameter exposure chamber.

I should mention again that this particle size is one micron. At a higher concentration, a white color obtains and not the blue coloration characteristic of the oil fumes of auto exhausts which are blue because they have a particle size of three-tenths of a micron.

In the rats, there is no effect observable between oil mist with ozone and ozone alone. Apparently, this dose of ozone constituted a very high lethal dose for rats that obscured any mild ameliorating effects of the oil. We thought there may have been some effect that was obscured. It cannot be a physical effect (as already shown). I will give you some reasons why we do not think it is a physical or a mechanical effect of the oil.

We attempted to see what happens if we made a sequential run, and give the animals the oil mist, followed by ozone. This was done giving the animals a four-hour exposure to oil mist at the same concentration, and then exposing them to "lethal" concentration of ozone. You can see that there certainly is a reduction in effect. It looks as though there is an amelioration in the effect. This was also brought out in the study done also in a sequential way, but with a little longer interval between exposures.

Table 2.

EFFECT OF MOTOR OIL MIST (SAE 15) ON 4-HR. $LC_{50}$ OZONE IN RODENTS OIL MIST CONCENTRATION 700 $mg/m^3$

| Animal Species | $O_3$ Concentration, ppm Av. | Range | CT ppm-hours | MORTALITY Number | Percent |
|---|---|---|---|---|---|
| | | Simultaneous Oil Mist and $O_3$ | | | |
| Mouse | 4.0 | 3.1-4.6 | 16.7 | 10/20 | 50% |
| Rat | 4.0 | 2.8-4.9 | 15.9 | 5/8 | 62% |
| | | Oil Mist Followed Directly by $0_3$ | | | |
| Mouse | 4.1 | 3.5-4.7 | 16.9 | 15/30 | 50% |
| Mouse | 4.1 | CONTROLS | 16.0 | 6/10 | 60% |
| | | Oil Mist Followed in 18 hours by $0_3$ | | | |
| Mouse | 3.8 | 3.1-4.6 | 16.1 | 10/32 | 31% |
| Mouse | 3.8 | CONTROLS | 16.1 | 12/18 | 67% |
| Rat | 4.0 | 2.9-4.9 | 16.1 | 5/5 | 100% |
| Rat | 4.0 | CONTROLS | 16.1 | 5/5 | 100% |

The next slide of motor oil (Table 2) shows a similar effect, but not quite as pronounced as with mineral oil. You wouldn't expect much difference. Actually, the composition of those two materials is similar except for the additives in the motor oil.

Now what it would be nice to see, as we go on with the studies, is whether other irritants like $NO_2$, $SO_2$, formaldehyde, and others will have their noxious effects modified by oil similarly. Another thing that is obviously desirable to do is to find an oil in which ozone is soluble. There one might find an interesting response.

In the histologic slides of animals exposed simultaneously to ozone and the oil mist, there was no feature in the lungs, trachea, and bronchi that was not observed in the ozone controls. There was somewhat less edema in the animals that were exposed sequentially, however; and also, the most prominent thing, was that there was less desquamation in the trachea and bronchi, which is characteristic of ozone exposure at these levels.

Despite the fact that we exposed these animals to relatively large numbers of particles, there were really not many particles in the lung. Actually, the exposure to the 400 milligrams per cubic meter of the oil at one micron average diameter and a density of seven-tenths, corresponds in cubic meters to 1.1 times $10^{12}$ particles. Knowing the minute volume of the rat lung and the number of particles that will be inhaled during the four-hour exposure, it comes out around 2.6 times $10^9$ particles. So you can figure out how many one can see under the microscope. It comes out that there are really not many particles in the lung. This is a really very important observation. It comes out, at the magnification that we used, around 70 particles per microscopic field because the mouse lung has a large surface area. The human lung has a surface area of about 90 square meters.

The mouse lung is very similar in dimensions to the human lung. The important point I want to make about this is that these calculations bear out what one sees under the microscope. Instead of being a complete coverage of the alveolar surfaces, as one might suppose from the large number of particles that the animal is exposed to, one can see just five or six in a microscopic field. This again rules out a mechanical blocking by the oil that might otherwise prevent the ozone from getting at the delicate alveolar epithelium and the capillaries.

We conclude, therefore, that if there is any mechanism for this change that we see here, it must be on a physiologic basis, and at least tentatively we assume that this is due to the calling forth of the macrophages. In some way these macrophages appear immediately in large numbers and this may act as a buffer to the ozone effect. They may give off some reducing substance that will tend to counteract the ozone.

The final paper on this morning's program is to be presented by Dr. Fred A. Bryan, from the Medical Center of the University of California at Los Angeles, entitled, "The Effect of Synthetic Air Pollutants Of The Hydrocarbon -Ozone Type Upon The Pneumonia Infection Rate Of Suitably-Exposed Mice: A Preliminary Report."

DR. BRYAN: Our work at the UCLA Medical Center is definitely preliminary. This may sound odd after a year and a half of work. When we started out, our intent was to find an objective means of measuring irritation in smog. We felt that there should be some way, if possible, to have a biological index which was objective in nature.

We first set up what we thought would be the easiest portion of the experimental procedure. That was to produce the various substances which we wanted to add to the chamber. We chose ozone, $NO_2$, and $N_2O_4$, hexene, and a mixture of hexene and ozone. In making the last mixture we used varying amounts of ozone and hexene and varied the time that the two components were allowed to react before they were added to the chamber and diluted. Our reason for the choice of substances was to be able to correlate any data with work that has been done by others in the Los Angeles area.

We developed and built a special octagonally shaped inhalation chamber with deflection cones to insure complete mixing of gaseous and particulate materials. The chamber is made of glass and metal and treated with a plastic material inside and is quite inert to ozone and the oxides of nitrogen. The chamber, about 50 cubic feet in volume, is easily cleaned and sterilized. We can get rid of infected material through the drain on the bottom which connects to the sewer system. Sterilization is accomplished by use of lysol spray followed by rinsing with warm water.

We used an aerosol generator for discharging a spray of pneumococci in the air. This generator is an adaptation of that described by Wilson of Rochester, New York. To maintain as high a concentration of pneumococci as possible, we were forced to develop a small pyramidal 7-liter plastic chamber which will hold 30 mice.

In developing the low concentrations of hexene, we developed a water-jacketed and accurately controlled piece of equipment, made entirely of glass in which we could control the temperature, maintain a constant level of hexene and a constant flow of dry gas to pick up the hexene vapor. In an eight-hour period, it is possible to maintain the level of hexene to within a five to ten percent variation. We can run it from as low as three-tenths of a part per million, to ten parts per million. By passing hot water through the water jacket we undoubtedly can go higher if we wish. There are three controls on the device. First, the temperature of the water jacket; secondly, the flow of dry nitrogen through it; and third, the volume or surface of hexene exposed to the stream of dry nitrogen.

We also had to develop a means of metering the oxides of nitrogen. We purchased $NO_2$ and $N_2O_4$ as a liquefied mixture in a cylinder from Matheson Company. Here we used a syringe drive, and a water-jacketed syringe to hold the temperature of the liquefied gases at about 15 degrees Centigrade. The drive is such that we can hold in the neighborhood desired, of from one-tenth of a part per million to one and one-half parts per million of $NO_2$.

The ozone generator is a modified copper sulphate solution core with oxygen flowing by it. This type was developed at Stanford Research Institute. It was found that as theequipment was used throughout the day, the temperature rose and the amount of ozone produced changed. We now have water jacketed the equipment and it holds very accurately throughout the day.

When this was completed, we began to work on means of infecting the mice. We reviewed the work of Baetjer and others who worked on this problem. We did not want to use intratracheal injection of the pneumococci because we didn't want to add any extraneous irritation except that due to the $O_3$, $NO_2$, hexene, etc. In the early stages we used an aerosol containing pneumococci. At first we had difficulty in obtaining usable cultures of pneumococcus type II. We finally developed a broth in which we could obtain maximum viable organisms growth in six hours. Now it is possible to start in the morning and be ready to add the organisms to the air of the chamber in the afternoon. The pneumococci maintain their virulence very well.

It was found that the aerosol generator, as described by the Rochester group, did not put out enough material, so we added three tiny pinholes to the one already designed in the equipment. This gave us quite a heavy aerosol. We are able to produce, in 7-liters of air a minute, a concentration of viable organisms that both by calculation from the amount of culture media lost in the aerosol generator found by weighing before and after a known time interval, and by air samples taken from the small plastic chamber, had 250 viable organisms per cc of air. We thought this should be quite satisfactory to cause disease. It did not.

Literature indicated that the administration of alcohol intraperitoneally would allow the pneumococci to take hold in the mice. We tried it. The results were very variable. When the mouse became infected, the result was septicemia rather than pneumonia.

Finally, we tried the method of placing a tiny drop of the culture on the nostril of the mouse, timing the placement of a drop to coincide with inhalation. We find that we can produce a very small drop of 0.015 cc with the use of a 26 gauge needle, a tuberculin syringe and a special screw driven syringe drive. One turn of the screw thread delivers a drop of .015 cc. At first we followed the method described in the literature and lightly anesthetized the mouse with intraperitoneal nembutal. We now find that we are able to work better with unanesthetized mice. Using the Klett colorimeter as a nephelometer, we can measure and control the concentration of the pneumococci in the broth media with a Klett reading of 100 we get 8-10 percent mortality in the mice. If we use a Klett reading of 180 we get 19 to 20 percent mortality. If we use a Klett reading of 225, we get 28 to 30 percent mortality. This work is quite reproducible. Using this method, we have one test run using one and a half parts per million of ozone. This level of ozone seems to have increased the mortality by ten percent in this one experiment. Now that we have developed the methods and the equipment we hope to be able very shortly to report whether or not the constituents which we are adding at the levels normally found in ambient air will show any measurable effect on the mortality rate.

DR. HAYES: As I understand, this tiny droplet is simply placed on the nostril and at least some of the mice inhale it in such a way as to get a true pneumonia.

DR. BRYAN: That is all. All of the 300 mice that we have studied with this method had pneumonia. They may develop a subsequent septicemia, but all that died have consolidation in the lungs.

MR. KRACKOW: Rather than my making remarks about this work, I was wondering if Dr. Ehrlich from the Armour Research Foundation wouldn't care to comment. I know that his laboratory has been working along similar lines.

DR. EHRLICH: In our experiments we were primarily interested in the effects of ozone on the susceptibility of animals to bacterial respiratory infections. In the experiments, mice and hamsters were exposed to ozone and challenged with aerosols of Klebsiella pneumoniae or Streptococcus species. Our results indicate, essentially, that exposure to about one part per million of ozone for three hours significantly increases the mortality rate from bacterial pulmonary infection; it also shortens the survival time. As a result of the exposure to bacterial aerosols, we had the infection confined primarily to the lungs. It was a true pneumonia. Continuous exposures to, I believe, around 0.5 parts per million for 100 hours induced the same effect.

In hamsters we observed quite an interesting phenomenon. When we exposed hamsters to the K. pneumoniae aerosol only, we did not get any mortality. We exposed the same hamsters to a concentration of ozone of approximately one part per million for three hours, and then exposed them to aerosols which were around $10^5$ organisms/ml and we got essentially an $LD_{100}$. In other wo-ds, all animals died. We had two bases for the estimation of bacterial concentration. One was the original culture, and the other was the inhaled dose. The original culture was usually approximately $10^9$/ml.

DR. HODGE: Would you like to comment on this, Dr. Bryan?

DR. BRYAN: I just wondered how you were able to obtain the aerosol that concentrated to 10 to the 5th power.

DR. EHRLICH: No, I am talking about the initial concentration, the liquid culture concentration.

DR. BRYAN: You have no idea how many organisms then there were per cc of air?

DR. EHRLICH: We have, but I don't have the data with me.

DR. BRYAN: It begins to get rather difficult when you form it into aerosol, to get anything much over 200. Otherwise, you are getting such a concentration of the material or the broth that conveys the organism that it just throws it all out of proportion.

DR. EHRLICH: I have some data on LD. We have used a half-hour exposure to the bacterial aerosol, and the $LD_{50}$ value expressed as the inhaled dose was determined by collecting aerosol samples and then calculating it in terms of respiratory rate per minute. For our controls, $LD_{50}$ was 171 organisms. For exposure to four parts per million of ozone for three hours, the $LD_{50}$ was 10 organisms. For exposure to one part per million for three hours, the $LD_{50}$ was 131 organisms. For exposure to one part per million for 100 hours continuously, $LD_{50}$ was 19 organisms. And for exposure to one part per million for four hours, five times a week, for two weeks, $LD_{50}$ was 100 organisms. These values are for mice exposed to aerosols of K. pneumoniae.

DR. HEIMANN: We will now proceed with the next panel.

## PANEL III

## THE EFFECTS OF AIR POLLUTANTS UPON LUNG FUNCTION

DR. HEIMANN: Dr. Norton Nelson has agreed to be chairman of this panel.

DR. NELSON: It appears that we are advancing by slow stages from primitive forms of life to more complete organisms and, perhaps, if the program lasts long enough, we may even cover the "superman." However, this afternoon, the program is concerned primarily with organ functions of the intact animal and man. The title of the first item on the schedule has been revised by Dr. Whittenberger to read: "Methods For The Study Of The Effects Upon Lung Function Of Man Of Controlled Exposure To Air Pollutants: Preliminary Report."

DR. WHITTENBERGER: This is a small change in wording, but quite a large change in content. I did not anticipate the administrative delays which have occurred to prevent our reporting on what I thought I would be able to report on today.

First, we had difficulties with the liability insurance in connection with the use of human subjects. Then we had delays in obtaining approval of the contract.

Our facilities are now about ready, and I expect that we will soon be able to undertake studies to determine whether the observations that Dr. Amdur has made in unanaesthetized guinea pigs hold for man. In other words, does the effect of a low concentration of $SO_2$ on pulmonary resistance greatly increase when it is administered together with a low particle size aerosol? We expect to be able to study the effects of a number of individual gases, of combinations of gases, and of combinations of gases with particulates. The method of study that we propose to follow includes the use of a body plethysmograph, developed by Dr. Jere Mead and which differs somewhat from the one Dr. Comroe developed and that Dr. DuBois has been using in studies of air pollution.

With the body plethysmograph and the method of sampling esophageal pressure we will be able to measure the changes of total pulmonary resistance in response to inhalation of irritants. With this technique we can measure the pulmonary compliance or the elastic properties of the lung, the subdivisions of lung volume, the maximum flow rate, etc.The second part of our program is one in which we have made only a small start. This is the testing for use of simpler means of measuring pulmonary function, means which potentially can be used in community studies. These include timed vital capacity, maximum breathing capacity, maximum flows, pressures, and resistance, by methods that are simpler than those I mentioned first.

At this point I had better say that, whereas most of the other speakers today have emphasized that they were giving preliminary reports, what I am going to talk about in the next five or seven minutes is actually a report of somebody else's work, namely, Dr. John Clements of the Medical Directorate, Army Chemical Center.

Last year a similar conference group heard from Dr. Sim about the use of a simple method of measuring pulmonary resistance. He called it the Ainsworth technique. This technique was used in community studies in England and there was great interest in its potentiality. The basic principle of the method is one that has been known for about thirty years. This consists in attempting to estimate resistance from the change in pressure in the airway when air flow is stopped. Drs. Otis and Proctor were probably the first in the U. S. to develop a method for obtaining this information.

Otis' and Proctor's statement of the principle involved was that when respiration was occurring, the alveolar air pressure differed from the air pressure at the mouth by an amount which was related to the resistance to air flow at that time. If flow is stopped suddenly, there will be quick adjustment of pressure in the system so that the mouth pressure will be the measure of the total pulmonary pressure; and, if the volume of the alveoli is much greater than the volume of the conducting system, the adjusted pressure will be what the alveolar pressure had been prior to interruption. By repeatedly measuring the quick adjustments of pressure and plotting them against the flow rate at the time of interruption, a curve of resistance of the airway was obtained.

About five years ago, Dr. Mead and I compared resistance measurements obtained in this way with a method of measuring that, in addition to airway resistance, included the resistive component of lung tissue and, in part, of the thorax. We came to the conclusion that what the interrupter method was actually measuring was not just the resistance of air flow through tubes, but rather the total pulmonary resistance plus some small increment due to resistances of the thoracic walls.

This is fairly complicated business to explain, and I won't go into detail at this time. I think it is accepted now that what the method measures under specified conditions is approximately the total pulmonary resistance. What Ainsworth developed, and what Clements has improved upon, is a method which changes a very tedious measurement into a feasible method.

[A series of slides was used to illustrate the Clements airway interrupter valve and manometer system for estimating pulmonary resistance.]

The next slide shows measurements obtained by two methods, the esophageal pressure method and the interrupter method. There is a good correlation in this rather small group of subjects.

I had Dr. Heimann try the method just before the program started, and he had a perfectly normal reading. This time (demonstrating) the reading is obviously erroneous. In some subjects it is impossible to obtain stable readings with this particular model.

My conclusion is that this may be a very useful apparatus if one uses it with due attention to all of the possible errors that can be encountered.

I brought along a few mouthpieces, so that at some time during the meeting, anyone who wants to get his resistance measured can do so.

DR. DuBOIS: I have always admired Drs. Whittenberger, Mead and Amdur's work on basic methods for measuring the physiological response of the lung. I think that they would agree that the physiological response may be triggered by inhaled factors which may produce an increase in resistance to air flow in the lungs, and that the physiologist feels that he might be able to help with instrumentation for measuring this response.

It had not been measured in the studies reported during the previous part of the meeting. So far, the investigators had been trying to assess the toxic reaction of materials in terms of pathological changes in the lungs. It is true that irreversible pathological changes may occur; but, it is also true that acute, reversible physiological changes may occur. The esophageal pressure method is a good basis for comparison of the physiological response of the lungs, and may be used as a sort of standard. It is relatively portable and requires standard equipment and balloons. We have used the plethysmographic method in Philadelphia, and are still using it for measuring airway resistance.

I would like to hear more about the possible errors of this modification of the interrupter method. For instance, is the flapping of the cheeks a sign of some malfunction in the human or the instrument?

DR. WHITTENBERGER: In the case of the second time that Dr. Heimann tried it (and every time that I try it), the apparatus responds about as follows: The first manometer gives a reading of the pressure related to flow through the external resistance. This should reach a steady value before the cock is turned which holds the manometer deflections until they are read. The second manometer is more sensitive than the first. Both readings should increase together and "hold", at which time one should turn the cock and make readings. When this happens, the resistance value is reliable.

When I am under test, the first manometer comes up and holds; the second one comes up slowly; but, before the second one gets to its high points, the first one starts down again. This probably relates to the fact that the actual resistance of the airway is a function of lung volume, and as I breathe out, my resistance is actually progressively going up. When I get below a certain value, it goes up fairly fast.

That is what I suspect is the most common source of error and it is probably related to the breathing pattern plus the high resistance in the pathway of the second manometer. I think the latter could be corrected.

The effect of the cheeks flapping synchronously with the interruptions is an important one. Dr. Clements has found that when he develops resistances of about 50 centimeters of water per liter per second, in a mechanical or electrical analog, the compliance of the cheeks is the limiting factor. In other words, the "tidal" volume of the cheek has to be exchanged before the pressure in the system comes to equilibrium. It is a lower error with normal resistance.

The third and most important limitation of the apparatus has to do with the distribution of gas in the lungs. If there are abnormal resistance pathways, as there are in emphysema and probably in "chronic bronchitis", (in the presence of abnormal resistances -- what we call discrepant time constants for different pathways in the lungs) then the equilibration of pressure within the lungs is not immediate. Instead of taking 5 or 10 milliseconds as it does in the normal lung, it may be so prolonged that no valid measurement can be obtained. Just what the limits are in terms of its experimental use, no one is quite sure yet. The apparatus has been used in England to study the effects of nerve gas, with resistance increases up to, I think two- or three-fold. Perhaps someone else in the Chemical Corps could answer that particular point better than I. We know that the apparatus goes into error progressively with very marked increases in resistance.

DR. NELSON: Dr. Meneely, would you care to comment?

DR. MENEELY: I have had very limited experience with this approach to the problem. I think everybody feels that airway resistance measurements would be a wonderful thing to have available, if it could be reliably determined. I think that self-contained in the demonstration here we have to recognize the question of whether this is a final method of doing it.

DR. NELSON: Our secretary, Dr. Roberts, has asked to comment.

DR. ROBERTS: Regarding the difficulty of taking those two different readings: I think that the causes of error lie in the gauges. Dr. Clements is working on that problem now by enlarging the pressure taps so as to improve the response of the gauges. This is the way he explained it to me just a few days ago, and I believe it is the only reason for it. I don't think that he encounters that difficulty when he uses electric transducers.

DR. NELSON: If there are no more comments we can proceed to the second presentation, which is also from Boston, a "Study Of The Effects of Controlled Irritant Air Pollutants Upon Experimental Animals: An Interim Report," by Dr. Mary Amdur:

DR. AMDUR: We have over the last three years worked out a means of measuring the mechanics of respiration in unanesthetized guinea pigs, and we have used this simply as a tool to evaluate response to irritants. Because it would take up the full time that I have been allowed, I will not describe the methods I used. However, I may say that three measurements, intrapleural pressure, tidal volume, and the rate of flow of gas in and out of the respiratory system, are made. Having those three measurements I can then calculate resistance and compliance of the lung. We have found that resistance to air flow is probably the simplest thing to use since it appears to be related to different irritant concentrations. Having set up the method, I turned back to an item that is a problem in air pollution studies, namely, the effect of aerosols on the response to irritant gases. Today, I shall talk about some of the data I have in that regard and some, possibly wild, interpretations that I have made from the data.

Initially we will talk about individual concentrations of irritants. The first slide is a plot of resistance in the control period, the exposure period, and the post-exposure period. The irritant is sulfur dioxide gas at concentrations of about two partsper million. The aerosol I now use is sodium chloride, definitely sub-micron in size. The sodium chloride itself produces no response. The sulfur dioxide produces some response which returns to the control values within a hour afterward. When you add the aerosol, you get slightly more response, and, interestingly enough, it fails to return to the control values.

The next irritant that I tried was acetic acid. Here we used concentrations of about 30 parts per million and, again, the same levels of sodium chloride aerosol. In this case, however, there was no difference in the level of response at the end of the hour, whether the aerosol was there or not. With the gas alone, the resistance level returns to control values an hour after exposure and when the aerosol was added, the level stayed up.

The third gas that I worked with was formaldehyde. Here, again, we have the sodium chloride by itself doing nothing, and formaldehyde plus the aerosol giving greater increase in resistance and failing to return to control values.

The next slide also shows formaldehyde. In this case I reduced the exposure to three-tenths and six-tenths of a part per million. The six-tenths level by itself does nothing. Neither does the sodium chloride by itself. When you combine the two, you get a marked response and, again, you see the reaction continued after the exposure ended.

The three gases, $SO_2$, acetic acid and formaldehyde, all seem to be similar in the presence of the aerosol, in that you have the continued reaction after you stop the exposure. They are different, however, in the sense that the sulfur dioxide and formaldehyde produce an appreciably greater increase in expiratory resistance when the aerosol is used as an adjuvant, whereas the acetic acid does not cause such a reaction. When this happened, I had to throw out a lot of pretty theories and look around for something else. Let's look now at the dose-response curves and see what we can make out of it.

This is the reaction with sulfur dioxide alone, plotting parts per million against percent increase in resistance at the end of an hour. The next curve shows the reaction due to sulfur dioxide plus the small particle size of sodium chloride aerosol. (The greater response in the presence of the aerosol is there all along the line.) When I use a larger particle size aerosol, however, I get no change in response.

You can look then at these two curves and compare them in terms of what concentration would give you an equal response. This is shown in the next slide in tabular form.

Table 1

| PPM $SO_2$ with NaCl | PPM $SO_2$ alone giving same response | Ratio of these - concentrations |
|---|---|---|
| 250 | 800 | 3.5 |
| 90 | 300 | 3.3 |
| 26 | 110 | 4.2 |
| 8 | 90 | 11.1 |
| 2 | 70 | 35.1 |

If you have 250 parts per million of sulfur dioxide plus sodium chloride, it gives you the same response as 800 p.p.m. alone. The ratio turns out to be three and a half to one. This continues to be so for higher concentrations, but not for the lower levels; and that was curious.

Then I thought that it had been suggested that an irritant *aerosol* possibly would act differently than would an irritant *gas*. Probably adsorption of the gas on the aerosol would act overall as if it were an irritant aerosol. So then I said, "I have done sulfuric acid mist, and I have a curve for that." And, here again is sulfur dioxide alone, and the sulfur dioxide plus aerosol and sulfuric acid mist. Then I compared those curves in the same way. I found that if I compared the sulfuric acid aerosol response curve with the sulfur dioxide gas curve, I got the same sort of bizarre thing. In other words, in that case it was equivalent to about 15 to 20 times that amount of sulfur dioxide at the high end of the curve and, then as it went down, it was equivalent to a lot more than you would have predicted; whereas, if I compared the acid mist curve with the gas plus aerosol curve, that was a perfectly straight line all the way across. In other words, the two appeared to behave in the same way.

So from that I thought that possibly the sulfur dioxide gas had got converted to sulfuric acid mist, which is more toxic. And then I thought that since acetic acid could not get converted to anything more toxic, maybe that's the difference.

Then I said, "Well, formaldehyde could go to formic acid, which is more toxic; so let's see what happens with formaldehyde and formic acid." Here we have the curve for formaldehyde alone, and here we have formaldehyde plus the aerosol. Again the curves compare in the same way. Then I did the formic acid, and, as you can see, the slopes of the formaldehyde plus aerosol and the formic acid curves are the same.

Too recently to put on a slide, I have done two points on the curve in which I have added the aerosol to formic acid, and it simply takes the points from here, and picks them up and puts them on the curve above. That's the collection of data that I have.

From it, all I can say is that it appears that when you combine formaldehyde with an aerosol, the thing you are looking at is a response to small amounts of formic acid, and that it appears to be a similar picture with sulfur dioxide and the aerosol.

I differ from Dr. Stokinger in that he has no proof of solubility or absorption, and he has sense enough to say that he doesn't, and that that can't be the explanation. I have no proof either, but, all I can say is that biologically it looks like it.

DR. MENEELY: Is it your impression, Dr. Amdur, that the colloids have the gaseous component adsorbed on them to any extent? Do you have any evidence on that? Or do they seem to be independent operators?

DR. AMDUR: The only evidence I know is the work of Johnstone at the University of Illinois. He did some work in which he used particles containing manganese salts and sulfur dioxide gas. He found that there was adsorption of the sulfur dioxide on the particles and conversion of the $SO_2$ to $SO_3$ and to sulfuric acid in that case.

DR. MENEELY: The thought I had revolved around this: if you put an electrolyte into the lung, whether you put it in in the form of an aerosol or in the form of pouring liquid down the trachea of an anesthetized animal, the electrolytes disappear at a very fast rate. For example, sodium chloride in distilled water will disappear from the alveolus of the dog with a half-time of about three and a half minutes. On the other hand, if you put colloidal materials, say, radioactive colloidal gold or many other colloids, down in the lung, they will disappear with half-times which may range on out into weeks.

I think Curtice's findings were half-times for disappearance of protein from the lung of the order of half-hours and hours. The reason for this is that the electrolytes go directly from alveolus to blood stream; whereas, when you put a colloid down, it does not go directly into the blood stream, it goes into the interstitial space of the lung, leaves the lung via the lymphatics and so is transported to the blood.

This can be clearly shown in the case of protein, and again in the case of colloidal gold. Any colloidal gold that gains access to the blood stream turns up in the liver like any other colloidal material which gets into the blood stream. And if you put colloidal gold down in the lung of the dog, and it does not show up in the liver, that is, in effect, a guarantee that it has not gone directly into the blood stream. It is such a big, lumbering thing that it takes a very long time for it to make its way up the lymphatics, actually taking a week or two to get into the lymph nodes. Whereas, protein moves up in a matter of an hour or so.

It is hard for me to imagine sodium chloride sitting around as a colloid very long in the interstitial tissue. But one might wonder whether this might enable one to build up a higher concentration of the material in the lung -- an instantaneous higher concentration locally when a sodium chloride aerosol particle first comes to rest on the alveolar surface, delivering its adsorbed cargo of $SO_2$ or $SO_3$ in one sharply localized spot.

DR. GOLDSMITH: I would like to ask Dr. Amdur if she has any information on the effect of humidity on the phenomenon that she described.

DR. AMDUR: No, I have not tried different humidities. Sodium chloride will certainly absorb water. Possibly when it absorbs water, it also takes other gases.

DR. DuBOIS: Again, I would like to add my admiration for this method. Here are studies which nobody has been able to do before, largely because there has not been a good method for taking an intact conscious animal, and assaying pharmacological effects in terms of a very precise change in airway resistance. All the old methods had complicated anatomical preparations in which the lungs were in a bad state to begin with. They were not measuring what they were supposed to be measuring.

The reason for needing such a preparation as Dr. Amdur uses is because many ideas have arisen as to what particles ought to do in the trachea, and where they should fall out in the bronchi; but it is largely theory, and the exchange of moisture between the particles and the surface of the trachea or bronchi is approached much better in this type of experiment than it is in theory. Conditions of humidity, and the condition of the mucosal surface are so very variable. In such studies, it is true we don't precisely know whether the response is due to bronchospasm, mucosal edema, or mucosal congestion. It could be any or all. But, for purposes of bio-assay of this sort, I am not sure that it matters much.

We also don't know whether complications in this type of animal in the form of atelectasis, obliteration of the bronchi, or peribronchial fibrosis might set in. These things, of course, would be very important in man.

DR. NELSON: I would like to raise a question myself.

Have you chemically analyzed any of these aerosols to determine whether oxidation to sulfuric acid or to formic acid occurs, in fact?

DR. AMDUR: I have had no luck with what I have tried. However, there is a method -- it is either Gerhardt and Johnson or Gillespie and Johnson; I forgot which -- where they impregnated a film strip with an indicator and then picked it up. And I thought of setting that up and trying it.

DR. DAVIES: Did you get some sulfuric acid with the $SO_2$?

DR. AMDUR: I would think so.

DR. NELSON: Johnson's group has carried out work on this, but my understanding is that the oxidation is really quite slow in the absence of a catalyst. That is one of the factors that came out with the contribution of sulfur dioxide to the problem in Los Angeles. Is that correct, Dr. Chambers?

DR. CHAMBERS: I think you are talking of relative speeds of reaction. As a matter of fact, the reaction of $H_2SO_3$ to $H_2SO_4$ is very fast indeed, but not nearly as fast as it is in the presence of a catalyst. Both of them would be so rapid that I wouldn't expect the presence of much $H_2SO_3$, as Dr. Amdur suggested.

DR. NELSON: I might anticipate a comment that I am sure that Dr. Goetz of California would make if he were here. Although I am not familiar in detail with his work, I can say that he has recently given thought to the question of potentiation of toxicity from the simultaneous inhalation of aerosol and gas. He has developed a concept based on physical and physio-chemical analysis, which he believes would lead to a localized, high-intensity point of contact, which he thinks may in part explain the potentiation of the sort that Amdur and LaBelle observed.

DR. VORWALD: We have studied the exchange between agents and other substances. Although I have nothing concrete to report, I can indicate a recent observation where we have used phenol and phenol "attached" to activated carbon particles. The mechanism of attachment is obscure. But our preliminary observations would indicate that vaporized phenols attached to carbon particles are much more toxic when introduced into the lung that is a comparable concentration of phenolic vapors suspended in distilled water.

DR. NELSON: The next presentation is, "Lung Function Changes in Patients With Cardiorespiratory Disease Exposed to Naturally-Occurring Air Pollutants: Second Interim Report," By Geoffrey C. R. Carey:

DR. CAREY: By way of recapitulation of previous reports, the following two slides will give a summary of the three field surveys which we have carried out, to date, in Cincinnati. The general approach to this problem is that a number of cardiorespiratory patients, who are more or less confined to their own homes, are followed subjectively by means of diaries, and objectively by means of lung function tests, and by measurements of their environments, in an attempt to relate the changes in lung function and changes in the symptom "scores" in the diaries to the changes in the atmospheric variable.

The first slide shows the design of the three surveys, the first beginning in February 1955, the second in the fall of 1955 and the third one in 1956. The main difference in Survey No. 3 from the others has been that it systematically recorded gaseous acids in the homes of patients. Smoke was recorded in all surveys. The diaries have been progressively simplified as we went from one survey to the next. As far as the lung function tests were concerned, we stopped using the oximeter, early. We have developed a Bellows spirometer which has proved quite useful. I will talk about that later. The chief point of our third survey has been the development of the box-bag for measurement of carbon monoxide diffusion as a function of the lung.

The first two surveys provided half a million observations and the analysis of this was complicated by the fact that the patients were visited at irregular times. It was hoped that a large IBM computer would be able to handle the material but this hasn't been possible. Nevertheless, some of the data from Surveys I and II have been analyzed manually for comparison with Survey III, notably the diary and lung function data.

Survey III was organized on a much simpler basis, though the measurements probably have greater accuracy than before. Each patient was visited at the same time of each day, three times a week, and this provided a fixed time base and a better balanced experiment. As a consequence of this we were able to commence the multiple regression analysis as soon as our Burroughs E-102 machine was delivered to the laboratory in April 1957. At the moment we have completed about 1,500 out of a total of 4,000 individual regression analyses and the machine is on double-shift working. Preliminary analysis of the data seems to show that some of the objective tests, notably the timed vital capacity, are correlated significantly with atmospheric variables, typically after a lag of three to four days. In some cases the objective tests appear to be correlated with gaseous acid levels, considered independently of smoke, thus supporting our view that both smoke and gaseous acid should be measured in the homes of patients in such studies. These are preliminary findings only. Firm conclusions must await the completion of the analysis which is expected in about a year.

Now, I would like to say a few words on the measurement of the external environment. Observations of smoke and gaseous acids at our three stations suggest that the relationship of these two indices, smoke and gaseous acid, may vary considerably from one part of the city to the other. In the center of the city, the correlation is quite good, although there is a lag of two or three hours between maximum smoke and gaseous acid levels. At the Medical College and Abbe Observatory, respectively two and four miles north of the city, the two indices are not so well correlated, and the lag is reduced from one hour to even zero at times. Gaseous acid levels are not sustained for quite as long as the smoke readings. In addition, the ratio of smoke to gaseous acid is proportionately greater when pollution is light, particularly in suburban areas. Concentrations of smoke and gaseous acid may vary considerably within a single large building. For example, the men's ward in an old persons' home had consistently higher smoke and gaseous acid than did the women's ward. The men liked fresh air and opened their windows. The ladies hated drafts and kept their windows shut. Hence, the difference.

A word on patient diaries. We have continually tried to make the diaries more simple for the patient to use. But, even now 32 entries a day are needed for each patient. This may tax the intelligence or the good will of some patients. Nevertheless, only about three percent of diary sheets had to be discarded in the last survey. We score the diary sheets in this way: A score of minus one point is given when a symptom occurs "less than usual," zero for "usual," and plus one when a symptom is "more than usual." Six-hourly and daily totals are computed for all symptoms combined, and daily totals are computed for each patient with respect to each individual symptom. All other things being equal, the standard deviations of each patient's score should be relatively constant from month to month. We found, however, that this was not the case.

In the first place, 40 percent of the patients showed a progressive decrease in the variance of their symptom scores, commencing during the second month of each survey. This phenomenon is probably due to the patient losing interest in the survey rather than to his progressive adaptation to atmospheric contaminants, since this deterioration occurs irrespective of whether the survey begins in January, September or October. Secondly, some of these patients participated in successive surveys, and appeared to regain their interest during the intervening period. But they always deteriorated in enthusiasm in the same way on the next survey. When the medical staff visited the homes of the patients more frequently, as they did in Survey III, the variance of the symptom scores on these patients didn't deteriorate as rapidly as those before.

A number of patients showed some relationship between symptom scores and smoke density. The slide now on the board shows a similarity in magnitude of the smoke and symptom peaks during the whole of Survey III for one particularly good observer. Symptom lag is one to seven days. Now of course this is not nearly so precise and striking as the curves which Dr. Lawther has recently published in the British Medical Journal; but there is a sort of correspondence between symptomatology and smoke levels.

This slide shows the Bellows spirometer which we used in Surveys II and III and which has proved to be very satisfactory and robust. When used in the field over the three-month period, and used by practical nurses, the standard deviation of an individual total vital capacity measurement is plus or minus 330 milliliters --- rather good for use in a field survey of this nature.

Another lung function test which we have been developing is the box-bag technique for carbon monoxide diffusion. This slide shows an early model of the box-bag. Dr. Shephard, my associate, has now produced a box-bag with which the patient will approach the "steady state." It can be used for a test lasting about three minutes, and thus approaches the "steady state" for CO uptake. It can also be used to obtain single-breath measurements. The box-bag method in itself is competent to indicate the deterioration of a patient's condition with age and emphysema. The carbon monoxide uptake measurements are rather more useful than those of functional residual volume. One difficulty is, of course, that carbon monoxide measurements may be due to either an absolute defect of diffusion or to a deficiency in mixing. Dr. Shephard, in his paper, will indicate a method which he is developing to differentiate between these two factors.

Between October 12 and 17, 1958, at the beginning of the third survey, an acute thermal weather inversion occurred in Cincinnati. Peak concentrations of 0.4 parts per million of gaseous acid and 14.5 CO/1000 were recorded at night, but the levels of these contaminants fell to seasonal normals during the daytime. The average temperature was much higher and the humidity lower than in the London smogs. Six of our ten cardio-respiratory patients showed an increase in symptom scores five to six days after the first peak of the smoke record in their particular environment. Eight out of these ten patients showed a consistent and progressive fall in carbon monoxide uptake commencing on the 19th of October and continuing through until the 29th, at which time it began to come back slowly to normal. The departure of carbon monoxide uptake from normal is more than 2.7 times the standard deviation; so, it is difficult to attribute these findings to chance alone. It looks as if something of the same effect may have occurred during one period in November; but, what we are especially interested in, at the moment, is this prolonged fall in carbon monoxide uptake.

DR. MENEELY: I admire anybody who has the courage to tackle this sort of work. Of all the fields in which one is saddled with many variables, this is certainly one of the major ones. Anyone who has attempted to obtain base lines for experimental studies on patients who have chronic respiratory or cardiac impairment, is well aware of the extraordinary variability. Yet in spite of that they have begun to show signs of getting encouraging results. I think it would be out of the way to try to comment seriously on the findings. Dr. Carey doesn't really offer findings. He simply indicates directions in which they are going.

DR. DuBOIS: I wonder whether the statistical analysis takes into account the individual subjects that have a really significant change, if there are such individuals. It seems to me that those would be the kinds that one might see in a medical situation. Secondly, the CO uptake test that I gather takes three minutes, includes the ventilation of the dead space as well. This then would involve a mixing problem that may be creating the basic difficulty.

There are actually two schools of thought about CO diffusion in emphysema, of which Forster represents one. He believes that it doesn't actually fall in most people with emphysema. Bates, with his box-bag system, feels it does fall. The same happens with old age essentially. There is often a question of methodology as to whether there is a real diffusion impairment.

In regard to the vital capacity recordings, I am not quite clear of what the findings are up to date, except that the standard deviation is 330 milliliters. That seems to be a rather large variability, particularly if you are looking for changes in a subject.

DR. MENEELY: Dr. Nelson, I have one other comment I would like to add. One of the biggest single difficulties in this whole circumstance is that here the patient is usually aware of what is supposed to be the genesis of something which will produce physiological changes. This is, of course, the biggest invitation to psychic stimulation to bronchial activities and other sorts of symptoms.

DR. CAREY: So far as the lung function tests are concerned, there is certainly some tendency for sub-psychological consideration to come into it. In other words, a patient may not want to try so hard on his timed vital capacity tests. That is quite possible. Similarly, on the pulmonary pressure tests which we did, the value of that test is probably limited by the unpleasant sensations which the patient undergoes rather than any other factors. So motivation is another factor there. On the box-bag, however, it is very difficult for the patient to "fake" his results. He doesn't understand enough of the fundamentals of the test to change it very much; and even if he did try to do so, the test is still objective.

There is the difficulty, of course, of whether the defect in carbon monoxide uptake is due to diffusion difficulties or to mixing; but, no matter what it is, what we are concerned with in the surveys primarily -- not finally, but primarily -- is: Does atmospheric pollution cause any difference to these patients? And no matter why it occurs, if it does occur, that is in itself significant. The box-bag may not be a pure test. It may be a hybrid one in its present form; but, it still is showing up some results. The analysis takes care of all the patients by computing their standard deviation throughout the survey. Each patient is an experiment in himself and is measured about his own mean.

DR. WRIGHT: I would like to make a comment in the form of a question. Perhaps I missed at the outset whether or not these patients are primarily pulmonary disease with cardiac complications or whether these are a mixture of people with heart disease who have pulmonary disease. How many people are in your series?

DR. CAREY: In the last survey there were only ten patients. Half of them were primarily pulmonary cases with emphysema, and five were primarily cardiac.

Dr. Shephard reminds me I haven't met one criticism on the vital capacity measurement -- the 330 milliliters. This is taken through the whole survey period and is the standard deviation for the whole survey. It may include some effect due to air pollution which will only show up in the multiple regression analysis. These are untrained subjects, and I believe that for an ordinary physiologist taking untrained subjects in the field, the standard deviation may be about 200 milliliters, but I don't know whether that is correct.

DR. WRIGHT: Dr. Nelson, May I ask another question? Do you find any differences between those two groups of patients -- the primary cardiac and primary pulmonary patients? Do they act differently?

DR. CAREY: No.

DR. NELSON: The next presentation is also from Cincinnati, and has the title, "Partitional Respirometric Analysis of Responses To Naturally-Occurring Air Pollutants," by Dr. R. J. Shephard:

DR. SHEPHARD: In the previous presentation, Dr. Carey referred to the recent work in his laboratory that has demonstrated, in sensitive individuals, a clear-cut response to quite low concentrations of naturally-occurring air contaminants. This was shown experimentally as a decrease in carbon monoxide uptake. Interpretation of this interesting observation is complicated by the fact that abnormalities of either gas distribution or diffusion could be responsible for this change. It seemed possible to us that the field use of the technique of "partitional respirometry," as originally introduced by Hatch and Cook in 1955, might help in the elucidation of this change. This method has therefore been subjected to careful evaluation in the laboratory.

When this technique was first introduced, the limitations of gas analysis made it necessary to carry out three independent experiments, using gas mixtures containing carbon monoxide, acetylene, and ether, in turn. More recently infrared equipment permits the serial analysis of all three gases.

The present report discusses some preliminary findings with this new equipment and suggests modifications of technique which may give meaningful results, both in the laboratory and in the field.

A diagram of the breathing circuit that we used in the laboratory is shown in this first slide. The composite gas mixture of ether, acetylene and carbon monoxide was stored in a Douglas bag. The subject breathed through an ordinary mouthpiece and the expired gas passed to a small mixing chamber and then through the three infrared analyzers.

There was a considerable loss of ether during the period of storage, amounting on the average to a change in concentration of 4.6 percent, plus or minus 0.7 percent, in a series of 20- ten-minute experiments. There was a smaller loss of carbon monoxide amounting to 0.4 percent, plus or minus 0.1 percent. There was no change of acetylene concentration. The expired gas mixtures were analyzed "wet," as it was found that drying agents removed quite a large proportion of the ether from the mixture. "Dummy-runs" on subjects breathing room air served to indicate the effects of both water vapor and carbon dioxide on the infrared analyzers. After passage through the analyzer the gas was returned to the main circuit for measurement of ventilation, tidal volume, and respiratory rate by means of a differential spirometer. Gas was pumped from this spirometer at a pre-selected rate, in the range of six to nine liters per minute. This arrangement gave very low resistance to gas flow.

The analysis of partitional respirometry data is dependent on the extrapolation of the uptake of these three gases back to zero time. With ether, this procedure is fairly satisfactory. The two main components of gas mixing in the lungs procced very rapidly and reach insignificant levels in half a minute; and, the three main components of tissue uptake do not decline very greatly over the course of the first five or six minutes. If you add together these five components of the observed gas uptake, you obtain the predicted curve of gas uptake which is shown at the top of the next slide; underneath is shown (in the stippled line) an observed curve for one of our subjects; it is evident that if you take the period after completion of gas-mixing in the lungs, you get quite a satisfactory value for the gas uptake at zero time by extrapolating back that exponential curve.

With acetylene, as shown in the next slide, the position is much less satisfactory. The gas mixing in the lungs proceeds a good deal slower. The slow gas-mixing component is quite appreciable to about two minutes; and, the visceral tissues approach saturation point rapidly.

Looking at the predicted curve which is obtained by taking each of those five components of the gas uptake curve, you can see that no single part of the curve corresponds to a straight line exponential, and the portion of the curve which you use in extrapolation becomes quite critical. It can be shown, empirically, that the best value for zero gas uptake, after completion of lung mixing, is given by extrapolating the curve over the period one to three minutes. The use of the total experience of a 20-minute curve, as was previously suggested by Hatch, is obviously going to give values that are much too low for the uptake at zero time.

It is necessary to convert our measurements of ventilation to alveolar ventilation, and that requires a measurement of the dead space. Ether has previously been used for this purpose but we feel that it is difficult to obtain a representative sample of alveolar gas when you use something which is absorbed as avidly as ether. Furthermore, the results with ether can also be influenced by abnormalities of the ventilation-perfusion ratio, which is one of the things we are trying to analyze with this technique of partitional respirometry.

The ideal method is one that uses an inert gas; and, if studies are to be extended to rapid respiratory rates as are obtained during exercise, or to people with diseased lungs, it may be necessary to match gas densities. The density of nitrogen is quite similar to that of carbon monoxide and acetylene; and, argon, with a density of 39, would be suitable for the measurement of the ether dead space. With this technique of partitional respirometry, our figures show that young, healthy subjects have a ventilatory efficiency of between 75 and 90 percent. This is rather lower than the previously reported figures given by Hatch and Cook, and this is due largely to the fact that we use a different method of extrapolating the data back to zero-time. The present estimate of 75 to 90 percent agrees quite well with the recent estimate made by the blood-gas method of Sevringhaus and Stupfel. The effective pulmonary blood flow, as measured by our technique, averaged 5.5 liters per square meter of body surface per minute, a much higher figure than has been reported by Hatch. His figures were somewhere between 1 and 1.5 liters per square meter. Again, this difference is due to the method of extrapolation.

From our figures it would seem that a high percentage, perhaps 80 to 90 percent, of the cardiac output is effective from a viewpoint of gas exchange. This again seems to be in keeping with the results of recent blood-gas studies. A low effective flow was originally postulated because of the discontinuity of alveolar ventilation. However, during quiet respiration when the tidal volume is perhaps only a fifth of the total alveolar volume the effective contact time for alveolar gas is going to be about 90 percent of the respiratory cycle; and, even during deeper breathing a discontinuity of pulmonary capillary flow may compensate for a shorter contact time under those circumstances. In equalities of ventilation will reduce the apparent diffusing capacity, because little carbon monoxide will be distributed to the areas of the lung that may have a good diffusing potential. The ventilatory efficiency that we can measure with ether and acetylene mixtures is of little help in analyzing this, since this ventilatory efficiency largely reflects inadequacies of perfusion, whereas, carbon monoxide uptake for practical purposes is largely independent of perfusion. What we need is an accurate measurement of perfusion efficiency. This implies, in addition to measuring the effective flow, some measurement of the total cardiac output. For "absolute" work, cardiac catheterization will probably be necessary, but relative changes may be assessed by physical methods that measure cardiac output indirectly, such as the ballistocardiograph. Some measure of lung ventilation can also be obtained from helium mixing curves. The traditional point of comparison is the time or the number of breaths taken to reach 90 percent mixing. In this normal subject (as shown in this slide) you can see that this point of comparison indicates a rather low efficiency, 58.6 percent. The reason for that is that the choice of 90 percent mixing gives undue significance to the lower part of the curve.

An alternative method of presenting the data was originally suggested by Briscoe, Becklake and Rose. Here we have the apparent F.R.V. (slide). The curves show the course of lung mixing with different tidal volumes, assuming single chamber mixing in the lungs, and the broken line shows the actual course for the same normal subject. This subject had an effective tidal volume of 545 cc, and you can see that the behavior of more than half of the functional residual volume of the lungs is very close to a single chamber model. It is only over the upper part of that curve that it begins to deviate from the single-chamber model. Figuring the average efficiency for the lung in this way, you can calculate that it is at least 80 percent in this particular subject. The figure calculated thus indicates an upper limit for areas of the lung that are poorly ventilated. Of course, it does not take into account possible concomitant variations of ventilation and perfusion; nor does it indicate areas of the lung that are well-ventilated but over-perfused.

In emphysematous subjects, partitional respirometry shows a relatively normal ventilatory efficiency indicating an adequate blood supply to those areas of the lung that are ventilated. However, both the diffusing capacity and the effective pulmonary blood flow are reduced, illustrating the dual role of damage to the alveolar wall and poor gas distribution in the causation of this condition. The gross mixing defect in a typical emphysematous subject is illustrated in the next slide. In this subject, the mixing efficiency at the point of 90 percent comparison is no more than 15.5 percent. In the next slide is shown a plot the data by the method suggested by Briscoe and his coworkers. It is at once apparent in that slide that the mixing defect extends to a much larger proportion of the total functional residual volume. Effective tidal volume is there very low throughout the course of the mixing. For field tests, it was decided to modify the complicated apparatus we had been using in the laboratory, and to employ a modification of our portable box-bag as illustrated in the next slide.

This is basically the same as was used in our final field survey. One addition to it is the mounting of an auxiliary 30 liter bag on to the exterior. The subject is able to breath the test mixture from this auxiliary bag for a matter of three minutes; and, then he is switched into the box circuit for a further minute of breathing of the test mixture. One might think that in the helium mixing curves that you have just seen, this initial three-minute period of equilibration is too short; but, fortunately mixing proceeds very much more rapidly in the case of an absorbed gas. Carbon monoxide, in that same subject, is shown in the next slide. You can see that at the three and a half minutes the percentage of unmixed gas with carbon monoxide for that same subject is very small indeed. The other assumption which it is necessary to make in field use of partitional respirometry is that one can take an average value for the rate of tissue saturation when one is calculating extrapolation back to zero-time. Present experience suggests that the variation in the rate of tissue saturation between different subjects is not large and, indeed, the use of an average value may be preferable to attempts at extrapolating a rather irregular curve.

In summary, I would observe that partitional respirometry can add significantly to our knowledge of gas uptake processes, both in the laboratory and in the field. In cases of pure alveolar-capillary block, it can confirm the diagnosis by excluding concomitant abnormalities of ventilation and perfusion. In future air hygiene surveys it will be most helpful to know whether a decrease of apparent diffusing capacity is accompanied by a decrease of effective blood flow. However, the method does not seem to give an absolute value for diffusing capacity independent of ventilatory abnormalities unless the total cardiac output is also determined.

DR. MENEELY: I have one comment I would like to make.

When you assume a simple exponential curve for mixing, something which is linear on semi-log paper (indicating on blackboard), you have a differential equation:

$$-\frac{dy}{dt} = ky$$

This is based on the assumption that the rate of change of the concentration is proportional to the concentration. The solution is:

$$y = ae - kt$$

Suppose you were confronted with a problem of filling a large number of milk bottles from a single hydrant, running back and forth from the hydrant to the milk bottle. You would fill the milk bottles near you, finding it easy to fill them quickly. It would take longer to fill the milk bottles farther away. These milk bottles wouldn't exactly be compartmented. You would have to go farther each trip. You would have a continuum rather than a fast mixing and slow mixing compartment.

If you assume not only that the concentration diminishes with time in a manner proportional to the concentration, but also that the concentration diminishes with time at a rate which proceeds inversely with time. You find a different equation. Actually, you write the differential equation in this way (demonstrating) so that we have "k" sitting over it. The quantity $\left(\frac{k}{t}\right)$ is a function, and it gets steadily smaller with time:

$$-\frac{dy}{dt} = \left(\frac{k}{t}\right) y$$

The solution is:

$$\frac{1}{y} = c\,t^{k}$$

We have begun to find out that many biological processes mix this way, and mixing curves can be very closely fitted by this expression. We become rather dubious about the concept of individual compartments, of subtracting out single exponentials. For example, Walter Wilde substracted out some five from mixing of potassium in the blood of the rat for the time from two and a half minutes to 24 hours. I doubt if it is really that. I doubt that there are only five exponentials. I think it is more complicated. I think it is probably a continuum. Probably in the instant case we have a different proposition. We have several different cases. And this puts another complexion on it. We are giving a lot of thought to this aspect of the mixing problem.

DR. SHEPHARD: I think I would agree absolutely with what Dr. Meneely said. It is just a mathematical convenience to divide the lung into these different components. If you take a matter of five exponentials, you can add them up. If you take ten, I suppose you could add those up. But, if you have got to take an infinite number you are going to have trouble.

All that I was concerned with doing with these different components was to establish the approximate form of that continuous curve. I wasn't implying that any definite volume could be contributed to any component. It is our belief that the course of lung mixing proceeds quite smoothly from the faster to the slow mixing component.

DR. NELSON: Is there any general discussion on this last presentation? If there is no further discussion, we are ready to proceed with the next panel.

DR. HEIMANN: The next panel is on Air Pollution and Eye Irritation, and Mr. Krackow of the Army Chemical Center has agreed to be chairman for this session.

## PANEL IV

## AIR POLLUTION AND EYE IRRITATION

MR. KRACKOW: The subject of Air Pollution and Eye Irritation certainly needs no introduction. This problem of eye irritation is generally the thing that most people immediately think about when the term "smog" is mentioned. I don't know the significance of the fact that we have only two papers on this rather important problem. Nor do I know whether this means that there isn't enough national effort; or that the amount of effort going into the study of eye irritation is disproportionate; nor whether there are too few people in the country interested or able to undertake studies in the field of eye irritation.

Dr. Leslie Chambers, who has been in the center of this question of eye irritation will start us off. He has been under a tremendous amount of pressure. He has to come up with answers to satisfy the local populace in Los Angeles. He will speak to us on, "A Synopsis of Eye Irritation In Los Angeles During The Past Twelve Months."

DR. CHAMBERS: I think that, perhaps, the reason that the eye irritation problem was given less attention on the formal program was because I spent such an inordinate amount of time talking about it last year. Dr. Heimann, in calling to ask if I would substitute for Dr. Merrifield who wouldn't be able to come to this session, asked that I should confine myself to those things that were new during the past twelve or eighteen months.

Most of the activities in the District in the past eighteen months have been confined to attempts to pin down, a little more definitely, the identity of the substance or substances causing the eye irritation response. Simultaneously, however, there have been a number of studies in the area aimed in the direction of improving the methods of measuring the eye irritation response, either in the field or in the laboratory. In particular, Drs. Frick and Merrifield have reviewed the 1954 data from the aerometric survey applying a little more refined analytical or statistical techniques, and Merrifield has carried out a study using a "captive" panel.

In both cases they attempted, by multiple regression factor analysis, to make some sense out of the numbers which have been accumulated. In talking to Dr. Merrifield about this just before I came out, he and I agreed that there is only one conclusion possible from the data at the moment, and that is that perhaps if the data had been adequate, the methods that have been applied might have "worked." But, for several reasons, the data have not been adequate.

In the first place, the 1954 data, we now know, were taken at an insufficiently wide spread of time during the day to give the proper correlations. In the second place, the measurements that have been made on the so-called physical parameters involved have been too non-specific to really expect us to anticipate any general correlations of a very close nature.

In connection with Dr. Merrifield's studies, unfortunately, he has depended on the ambient smog conditions in Los Angeles during 1956 and 1957, and, much to his distress, there have not been episodes of smog at reasonably high levels to use in his study. As a result, he has been somewhat handicapped.

Some work, along similar lines, has been done in our own laboratories. Syrek and his staff of our data reduction section, have completed and applied a computer program, using an IBM-650 in a multiple regression analysis of the eye irritation that has been experienced with respect to all of the other smog variables, including meteorological factors. I think I can summarize this study by saying that although several of the contaminants showed relatively high simple correlations with eye irritation, only oxidant levels showed any significant partial correlation when other contaminants and meteorological factors were held constant. And when I use the term, "any significant", I mean just that. The correlation is still not very good.

Dr. Orcutt attempted another approach to the statistical handling of the data by developing a quantal measurement of eye irritation. In that study he found a straight-line regression of the probit percent response on log concentrations of ether-soluble aerosols, oxidant, aldehydes, and particulate matter. This was very good, however, it was not good when we began to examine the 1957 Fall data, at which time we had started collecting data throughout the 24 hours. We found that we had perfectly nice correlation if we confined the measurements to the period of time from about 8:30 or 9:00 o'clock in the morning until 4:30 in the afternoon. When we began to examine the correlations "around the clock" with the data collected, particularly in the early morning hours and the late evening hours, we found there was no correlation whatever. The one thing that can be concluded from this study is that in all probability one does not get eye irritation in our situation unless a substantial amount of ether-soluble aerosol (particulate matter) is present. On the other hand, one can have high ether-soluble aerosols early in the morning, prior to irradiation, without having any eye irritation. This seems to indicate that statistical procedures aren't worth the time it takes to work them out, unless you have data which completely describes the situation.

Evidence bearing on the identity of the eye irritant has been developed by a number of investigators, in particular Drs. Goetz and Stevenson working at Cal-Tech. and Drs. Doyle and Renzetti at the Air Pollution Foundation and the SRI Laboratories. They have produced some data with respect to the possible participation of the aerosol fraction in the eye irritation phenomenon. Dr. Goetz' method, in particular, is of interest. With his particle concentrometer he has been able to demonstrate that the total removal of particles down to sizes of .01 microns or below, removes the eye irritant almost entirely from the irradiated automobile exhaust. Under other conditions, in which the handling of the gas was not as well controlled so that the temperature of the system rose during separation of the particles, the fractionation was by no means complete. Only a small part of the eye irritation potential was removed. This could be interpreted to mean that the fine particulate matter is associated with the irritant and that the irritant (whatever it is) tends to be volatile and tends to be released if there is temperature elevation.

It was also of interest that at least in the automobile exhaust system the increase in eye irritation produced upon irradiation seems to parallel the growth in size of particles up to a size of approximately three-tenths of a micron. In the original auto exhaust there is a characteristic distribution of particles clear down the spectrum; but, on irradiation the number of particles appears not to increase substantially, while there is a tremendous increase in mass of particles at the three-tenths micron size range. This again would tend to associate eye irritation with the aerosol.

The association of the aerosol with eye irritation has come to our attention in another way. During the course of investigations of the lead content of the atmosphere, Mr. Mayrsohn of our laboratory was adapting the polarograph to the determination of lead at low levels of concentrations and applying it to aqueous extracts of the so-called ether-soluble fraction. This material was collected on glass fiber filter, extracted with ether, and a portion of that extract dissolved in water and examined polarographically. Under those conditions he found a half-wave potential at about one to 1.03 volts which seemed to increase in amplitude with increases in the intensity of eye irritation. Furthermore, the degree of the light scattering that was occurring in the ambient smog seemed also to be correlated with the current amplitude at this voltage. The best identification of that polarographic half-wave that we have been able to make so far relates it to the organic nitro compounds, presumably the unsaturated type of compound and possibly unsaturates containing a terminal carbonyl grouping. As I mentioned this morning, the olefins or nitro-olefins that have been studied by Dr. Deichmann and, to a limited extent by ourselves, also show a similar half-wave potential, so that there is a possibility that analytical procedures for this class of material can be developed, provided the method proves to be sufficiently specific.

There are two or three other things I would like to add here. In the first place, the suggestion inherent in Dr. Amdur's report that formic acid may be involved is one which keeps coming up, and one which we, on the basis of analytical evidence, are inclined to believe has possibilities.

The infrared analysis of the reacting systems involving olefins and oxides of nitrogen (or ozone) show, much to our surprise, a very small amount of formaldehyde as an intermediate in the total photochemical oxidation; but, they do show a substantial component of formic acid. This is, accompanied by an increase in light scattering, which indicates the formation of particulate matter within the range in which Dr. Amdur is working. I will add that formic acid is identified in the Los Angeles atmosphere in concentrations which, if adsorbed on particles, might prove to be interesting from a standpoint of eye irritation. This needs to be explored much further. On the other hand, the evidence that we have so far with regard to the laboratory formation of the irritants, either in the field or in automobile exhaust systems, indicates that the process of formation of the irritants utilize $NO_2$, first of all. By emphasizing "utilizes," I mean it uses it up. $NO_2$ is apparently not acting simply as a catalyst.

It also utilizes the olefins which are present in those systems. We have demonstrated this recently with a new olefin recorder, which is continuously recording the few parts of olefins perhundred million which exist in the atmosphere; and the behavior of the olefins with the $NO_2$ is consistent with the view that there is a reaction between them that is resulting in the phenomenon we call "irritation."

There are other properties here also. As the olefins and the oxides of nitrogen are irradiated there is an increase in light scattering due to the formation of aerosols, the particles being predominantly in the .3 to .4 micron region. This phenomenon is observed during smog.

Another phenomenon that has to be tied in with identification is the observation that the irritant, whatever it is, is transient. It forms; it then disappears. Evidence from the SRI indicates that the half-life of the irritant in automobile exhausts may be of the order of 12 hours. Of course, in nature, its half-life would be influenced by the degree of dispersal accomplished by thermal convexion and other meteorological conditions.

All of these phenomena have been tied together to indicate to us the necessity for looking very closely at all of the possibilities inherent in combinations of $NO_2$ with unsaturated hydrocarbons, the olefins in particular. It has been found that acetylene does not react, or does so very slowly. The double-bonded compounds react rapidly. None of the saturated or the aromatic compounds react at anything like the same speed as the olefins. The rates of reaction are tremendously different. As a consequence, we are concentrating the search for the irritant precursor on the unsaturated components.

There was an observation made a long time ago by Haagen-Smit which indicated that the degree of ozone production, and by inference the degree of eye irritation production in smog systems or automobile exhaust or any of the hydrocarbon systems that he studied, was related to the ratio between the hydrocarbon and nitrogen dioxide. This has been confirmed with respect to the eye irritation response. If there is too little $NO_2$, you get little eye irritant. If there is an optimal proportion of $NO_2$ with respect to the olefinic constituent, you get a maximum of eye irritation. If there is too much $NO_2$, the amount of irritant produced is reduced or completely absent. This might be expected if we are dealing with a combination between $NO_2$ and an olefin in which a lack of $NO_2$ would result in a possible accumulation of transient amounts of the mono-nitro compound. A large excess of $NO_2$ might result in rapid formation of a di-nitro (saturated) compound, which is not notably eye irritating.

Many of these phenomena fit together. I have presented a few of them here. Most of them can be supported. Some are still speculative.

DR. BRYAN: This subject has been one that has been kicked around quite a bit, in Los Angeles at least. While there has been considerable work on it, it still seems that an objective method of measurement is something we are still looking for. Most of our methods of measurement are subjective. That leaves much to be desired. It is true that attempts at the use of impartial panels have been made to measure the degree of eye irritation. It works, apparently, to a certain degree.

Since I thought that perhaps I didn't quite understand the subject I went to the chief of the Department of Psychiatry at our University and asked for some information concerning this type of thing. His opinion was that, with all the newspaper publicity concerning this and all the discussion that went on publicly, it was almost impossible to obtain an impartial panel for making measurements that really were, in any degree, quantitative. He thought that it would be necessary to obtain a panel from some other area, even if you wanted to try the panel procedure.

In a way, I agree with him on that, since there are many people whose eyes smart the minute that visibility is reduced, and this occurs quite often. That can be fog coming in from the ocean but their eyes will smart.

I wonder whether Dr. Chambers has any information on this. Something was started on measuring the protein content of the tears, and I haven't heard any more on that recently. One other thing I would like to ask is this: In this work by Goetz, what is the temperature at which this separation occurs? It is extremely high, or would it occur as a separation from the particulate matter on just a real warm day?

DR. CHAMBERS: As I understand, it, the temperatues involved a change of only a few degrees from the ambient temperature level. So that we are talking here about a five or ten degree rise over the ambient level.

With respect to the protein measurements, I have not seen any further reports of work on the subject, although I understand some work is going on. Perhaps there is someone else here who can answer it.

I would like to make a comment on what Dr. Bryan said about the method. I think it is possible to criticize all of these subjective methods. Yet, I think we have got to bear in mind that we are measuring a subjective phenomenon, and it is a very real one to people who are involved. We have to take into account its psychological aspect. We have tried to assess the utilization of panels in various ways. Last fall we had from 40 to 100 persons near each of our monitoring stations and we have hourly records from each of those persons on their own response. These are untrained people who have simply reported subjectively, influenced by the newspapers, by fog, or by anything else. The result has been partially analyzed. We found that about 15 percent of the whole group never respond positively to any level of smog that we had. Another 15 percent respond to anything at any time, apparently. The remainder of them can be handled and the whole group can be handled statistically.

Comparative analysis of the results of that remaining 70 percent, alongside of the results obtained by recording the observations of a single trained observer at each of the stations, indicates that there may be nothing to be gained by the panel procedure; that a few people who are trained observers and who are selected to eliminate the completely refractory individual and the completely sensitive individual will give just about as good an approximation.

This may mean, simply, that the method has no inherent accuracy at all, as you indicate. But, so far as the laboratory is concerned, the method that was suggested, or that was used by Dr. Deichmann in his report this morning, is one that we have used very successfully. In that method we use 50-liter large-mouthed flasks with a stereoption viewer and slide built in to the large mouth of the flask. The individual puts his eyes up against the slide and we measure the number of seconds it takes before he experiences the first eye irritation. There is very little doubt in his mind.

This is a reproducible procedure. We have analyzed and we are continuing to analyze the procedure statistically by assorted panels, selected panels, uninformed panels, and, on the basis of temperature variations and so on. It appears that it is a straightforward, reproducible method of measuring eye irritation in the laboratory. Obviously, it is not applicable to a field situation.

DR. DEICHMANN: Dr. Bryan felt that perhaps some people in some other areas of the country ought to get into this problem. Maybe that is why we were picked.

It is my feeling that we have to use man as the experimental animal to get the answers that we want. We spent much time in considering various animal species and various tests that might be used for determining eye irritation. We finally decided to stop our animal experimentation and started to test for eye irritation in human subjects. It is my feeling that we will get the answer more rapidly this way than by sticking to experimental animals. We have found variations just as Dr. Chambers has. On the whole, however, the effects that we have noted in experimental subjects were rather reproducible.

There is one other point that I think we must keep in mind and that is that eye irritation is only one factor which is involved. In Los Angeles, I assume this is the pressing problem. We, at the University of Miami, are trying to determine the effects of the nitro-olefins on the whole body. Eye irritation may be the most obvious effect; but, I doubt that it is the only effect that is of importance to us all.

DR. GAST: I was certainly glad to hear Dr. Deichmann's comment that this is not the only effect of these irritants or toxic materials. I think that we have shown effects down at the tissue level. We have not been able to point to the specific reaction; but we hope to be able to do so by extensions of our technique.

I would like also to add that about six or eight months ago, using the simulated oxidant type pollutants that we are making, we verified on the polarograph the wave starting at about minus one; but it extends further than Dr. Chambers had indicated. I think that Dr. Mayrsohn has found, on further irradiation, that he does get some additional waves.

DR. CHAMBERS: On prolonged irradiation you move the wave gradually over to about 1.5 volts, as I recall it. I was referring, however, to what was found in the ambient atmosphere; and, in that case it seems to be held pretty constant at about 1.03 volts.

DR. GAST: Is he freezing that out with liquid air?

DR. CHAMBERS: No, this is not freeze out.

DR. SILVERMAN: I have a question and I would like to make a comment. The question is on this polarographic method. You don't obtain any curves unless you have at least 10-6 in concentration; so I assume this is long-period sample. The comment is in regard to eye irritation evaluations.

In World War I it was Professor Pearce of Western Reserve, I think, who was working for the Chemical Corps and developed a procedure to determine the irritating effects of several chemical warfare agents, such as chloropicrin and other lacrimatros. He found that the time one could keep his eyes open to a given concentration, when plotted for a number of subjects, resulted in a reproducible calibration curve.

DR. CHAMBERS: May I comment on the sample size? The sample that has been used here characteristically has been one taken on a high volume sampler running at about 50 cubic feet a minute for one to two hours. And, of course, that does provide a substantially high concentration of sample.

DR. SILVERMAN: Do you have any information on what the relative amounts of material would be if you calibrated it against, say, any one known nitro-olefin?

DR. CHAMBERS: No, sir, I haven't. This brings up a point I neglected to mention. Because Dr. Haagen-Smit found that ethylene did not give a substantially high ozone value in terms of rubber cracking in the smog reaction, it has been the custom to ignore ethylene in respect to eye irritation. We went back and checked that, along with other olefins, and we found, much to our astonishment, that ethylene appears to be almost as irritating in its reaction as any of the other olefins. This is very disturbing and very significant in view of the fact that the automobile exhaust, at least in the cruise cycle, may consist of 30 to 40 percent or more of ethylene, and this compound would therefore be present in perhaps a hundred times greater concentration than any of the other olefins, or all of the rest of them combined.

We are going to have to start considering the ethylene component as part of this reactive system, and that will raise the order of magnitude with respect to potential concentrations of these reactants.

DR. CAREY: In connection with the eye irritation, it is interesting to note that in the acute smog episode that we had in Cincinnati in October of 1956 there was complaint of eye irritation. A phone call told us that four office workers complained of lacrimation, eye irritation and some difficulty of respiration, around 11 o'clock on the 16th of October. As you will see from the figures in the slide, on October 16th, the ozone began to climb just at about the time that these office workers complained.

We sent our survey team down to the office in which these people were working and carried out our standard lung function tests on the complainants. The tests were repeated on them later in the year when there was no smog. We could not find any change or even dubious changes in lung function. Nevertheless, it is interesting that some of this lacrimation effect should occur in Cincinnati.

DR. CHAMBERS: In that connection, it is rather interesting that we obtained samples from Cincinnati, I believe, during that period, and from Philadelphia, and from a number of other American cities and London during a smog episode, and the polarographic half-wave, that I described at around one volt, occurs characteristically in all of them, but with reduced amplitude as compared with that of Los Angeles.

MR. KRACKOW: Our next paper deals with a study which takes on a more objective approach to this problem. "The Effect Of Noxious Gases On The Anterior Segment Of The Eye", will be read by Dr. Mettier.

DR. METTIER: The purpose of our study has been to determine whether there is any demonstrable effect of the various components of smog upon the anterior segment of the eye. We paid particular attention to its effect upon the corneal epithelium.

We have also had our share of difficulties to overcome in getting our project started. To begin with we found that the rabbits we use normally have a corneal epithelium that shows punctate staining with fluorescein. Also we found that the sawdust that we were using on the floor of our cages was getting into the animal's eyes and producing some superficial changes. We have had to overcome that and are now on the road to getting work done.

We use albino rabbits for our study. We have developed an animal holder that fits upon a slit lamp. The slit lamp is an instrument that consists of a bright illuminating source and a binocular microscope which can magnify up to forty times. We remove a measured area of the animals corneal epithelium, and then determine the regeneration rate of the epithelium into this denuded area. Also, the corneal thickness is measured with an instrument called a "pachometer". It will measure to an accuracy of 1/100th of a millimeter of corneal thickness. We are able to determine inhibition of the metabolic activity of the cornea by measuring the resulting change in thickness that occurs.

Filter paper is dipped into fluorescein and allowed to dry. This overcomes the disadvantage that may occur with the use of fluorescein, in solution, in that too great a concentration of the dye is achieved. By our method we can, by putting a drop of saline on this filter paper, get a small amount of fluorescein into the eye without having to be annoyed by an excessive amount. We use standard instruments, such as the one we use for corneal transplants, to circumscribe the area of corneal epithelium that is to be removed.

We use four rabbits in each "run" and are averaging a "run" per week. On the day prior to exposure the 10 square millimeter area of epithelium is removed from the right eye of three of the four rabbits. Two rabbits that have had the epithelium removed are then exposed to the toxicant, while the fourth rabbit is used as a control and is exposed to the vehicle of the toxicant which is San Francisco air.

Immediately following the exposure, the right eye is observed, the area of epithelium that is regenerated is measured, and a 7 millimeter area of epithelium is removed from the left eye. The reason we use 10 mm size the day before and only 7 on the day of exposure is that we have found that the right eye is generally regenerated to about a 7 millimeter area in 24 hours. The thickness of the cornea is measured with the pachometer and the epithelium that has been removed is given to a biochemist who studies it enzymatically. We also take some of the samples and make histological preparation of corneal epithelium. We enucleate these eyes at periodic intervals, to be studied histologically.

## TABLE I

Acrolein

3 mo. old rabbits exposed to 0.2 ppm for 4 hrs. Range of 5 experiments (20 rabbits).

| Treatment | Trephination | Chemosis | Iritis | Rate of Regeneration |
|---|---|---|---|---|
| Exposed | 10mm prior | I to + + + | 0 | healed 3 days |
| Control | 10 mm prior | 0 to I | 0 | healed 3 days |
| Exposed | 7mm post | 0 to ++ | 0 | healed 3 days |
| Control | 7mm post | 0 | 0 | healed 3 days |
| Exposed | none | I to + | 0 | healed 3 days |

So far we have run acute exposures with acrolein and with ozone. Table I is a summary of results using acrolein. It represents the average of five experiments, with a total of twenty rabbits. In the exposed group, in which the right eye had a 10 millimeter area of epithelium removed prior to the exposure, the day after exposure there was chemosis of the conjunctiva which ranged in degree from plus-minus to 3-plus. There was no evidence of iritis and the epithelium regenerated within three days. The only difference between these and the animal that was exposed to the San Francisco air alone was that there was a little less chemosis in the control animal. Healing went on at the same rate in both.

The animals in which 7 millimeter area of epithelium was removed following the exposure showed changes that were again similar, with a slight increase in chemosis being noted in the animal exposed to the toxicant. In the animal that was exposed, but had no trauma to its corneal epithelium, the chemosis was in the range of plus-minus to 1-plus.

The results from seven experimental runs with ozone, in which two parts to 2.4 parts per million of ozone were permitted to flow through the chamber for four hours, are shown in Table II. Here there has been essentially no difference noted between the exposed and the control animals.

## TABLE II

### Ozone

**3 mo. old rabbits exposed 4 hours to 2.0 - 2.4 ppm. Range of 7 experiments (28 rabbits).**

| Treatment | Trephination | Chemosis | Iritis | Pachometry (mm) |
|---|---|---|---|---|
| Exposed | * 10mm prior | + to ++ | 0 to ++ | 0.22 - 0.30 |
| Contol | * 10mm prior | + to ++ | + to ++ | 0.21 - 0.32 |
| Exposed | * 7mm post | 0 to + | 0 to + | 0.05 - 0.20 |
| Control | *# 7mm post | 0 to ± | 0 to + | 0.10 - 0.25 |
| Exposed | none | 0 | 0 to ± | 0.00 - 0.02 |

*Regeneration completed by third day

#Slight residual staining on third day in 2 of 14 eyes

We believe that the iritis that has been noted is probably the result of the actual trauma that the eye undergoes during removal of the epithelium.

We have also done some chronic exposures in which animals have been exposed to two parts per million of acrolein and of ozone for a period of thirty days. Here, again, no demonstrable pathology has been found, either on direct observation by biochemical enzyme analysis or by pathological study. We have also begun some acute exposures on medical students. Except for conjunctival injection and profuse lacrimation, which clears within five minutes, there is no demonstrable effect.

MR. KRACKOW: Dr. Mettier, you mentioned that some of the epithelium that is removed is subjected to enzymatic studies by the biochemist. What type of studies are underway in that area?

DR. METTIER: I am not a biochemist, by any means, and I will read what our biochemist said in his abstract:

> "It was felt that the most useful information regarding the effect of toxicants on the activity of enzymatic processes, might be obtained by measuring the activity of several representative enzymes related to the amount, or some direct function of the amount, of enzyme present. The choice of enzyme system is relatively simple, if one selects an enzyme from each of the major pathways --glucose monophosphate shunt, Meyerhof-Embden scheme and Kreb's cycle -- and picks dehydrogenases because of their ease of measurement in 'micro' amounts, and because of their sensitivity to inhibitors. The systems selected are glucose-6-phosphate, and lactic and maleic dehydrogenases. The measurement of the amount, or some direct function of the amount, of the enzyme is more difficult. Originally the biuret reaction for total protein was used. This test, when reduced to the 'micro' scale necessary for analysis of the small amounts of tissue available from epithelium scrapings, gave some unreliable results. Other methods now being tried are total micro nitrogen, dry weight, wet weight, and even calculated weight."

MR. KRACKOW: I think this report is rather significant. The field of eye irritation has, to my knowledge, never before been approached in a basic way.

This reminds me of the type of problem we have in skin irritations. Generally, the dermatologist hasn't been particularly research-minded, and it is only recently that we are getting into the problems of the physiology and biochemistry of the skin. I think the eye situation has taken a similar turn.

Dr. Mountain, I wonder if you would care to comment on the approach here, in terms of the biochemical situation?

DR. MOUNTAIN: All I can say is that it is the most logical and probably would be the most productive way of going at this. I think that if there is anything to be found, it will be found with this type of approach. I particularly like the idea of measuring some of these dehydrogenases. In World War II, the British studying the biochemical action of chemical warfare agents, followed that approach. It looked as though it was beginning to turn up some good information.

DR. STOKINGER: I would like to add a note in relation to ozone exposure. We have had some dogs on daily ozone exposure for three years to one part per million. Just before we came to this meeting one of our physicians examined them ophthalmologically, and could find no differences in the eyes of these animals from those of the controls in the laboratory who are not exposed to ozone. Dogs keep their eyes open during such exposures, whereas most of the other animals tend to shut their lids.

DR. PACE: I wonder if Dr. Mettier is acquainted with some work in this area now being done by a Russian group. Dr. Utkin of the USSR reported at a Cell Biology Meeting on some work he was doing in reference to eye irritation in white rats or mice. He used the mitotic index, and found a definite increase. The interesting part to me was that they have, evidently, been doing considerable work in this field. If you are interested, I can get the article.

DR. METTIER: I am not familiar with it.

MR. KRACKOW: I see Dr. Derryberry in the audience. I am wondering if you would want to make any remarks on some of the plant experiences. I know that at TVA you have had this type of situation. I wonder whether you have any information that might shed light on the question of eye irritation. Most of your compounds I know were $POCL_3$, or something of that type.

DR. DERRYBERRY: We have made no systematic observations of the kind of eye irritation that would, I think, lend itself to a contribution at this time.

MR. KRACKOW: If there are no other questions, I will consider this panel having completed its mission.

DR. HEIMANN: Thank you very much, Mr. Krackow.

Dr. John R. Goldsmith has agreed to be chairman for this next panel.

## PANEL V

## AIR POLLUTION AND CANCER

DR. GOLDSMITH: The first paper on this morning's panel will be given by Dr. Norton Nelson on "Consideration of Techniques Suitable For The Appraisal of Lung Carcinogens In Experimental Animals."

DR. NELSON: In presenting the work forming the basis for my report I should like to note that this has been a group effort between Dr. Marvin Kuschner and Mr. Sidney Laskin as well as myself. I am glad that in the modified program of this panel Dr. Gilliam has agreed to speak on the epidemiology of cancer. His report provides the background against which I would like to describe briefly some of our work.

One might say that there are essentially two primary ways of defining cancer incidence and cancer etiology. One of these is by epidemiology, or experience. The other is by experiment within the laboratory. It is this latter, that of deliberate experiment in the laboratory, that I would like to speak about today.

The laboratory techniques that have been available for examination of the lung cancer question have been many. Several of them depend on the use of tissues other than the lung for a test object. Skin-painting techniques, for example, have been widely used in the assessment of possible cancer-inciting agents that are suspected as being naturally active against the lung. Correspondingly, subcutaneous injection of the agent with the resultant development of a sarcoma has been used as a test procedure. There are some others as well. Lung tumor induction has been used in examination of this question. The mouse adenoma, for example, which has a moderate frequency of occurrence normally in certain strains of mice has been so used. In some mouse strains the spontaneous frequency is quite high. Histologically, mouse adenoma differs from the "lung cancer" lesion which is most prevalent in man, and particularly from that form of the lung cancer which has increased rather strikingly over the past thirty years, that is the bronchogenic variety. This in itself is not necessarily of serious moment. Nevertheless, if one looks at the question fully, the induction of adenoma does not appear to be the optimal test to use.

We felt, accordingly, that it was very desirable to examine the possibility of using a technique based on the induction of bronchogenic cancer in experimental animals. If such a technique could be devised, it could be applied to the assessment of suspected environmental agents for lung cancer. It is against this background that we have done our work.

We started with the observation, primarily of Andervont, (1939) that a thread carrying a carcinogen and pulled through the lung of the mouse produced some cases of bronchogenic cancer. This procedure was one of four that we employed. The other three procedures also all employed highly potent carcinogens as the suspect inciting agent. Our first objective was to induce the kind of tumor that we were interested in. The second objective was to study the pathogenetic factors which were responsible for successful results. This, we felt, would eventually lead to a laboratory assay procedure which, we would hope, could be applied to unknown and suspected materials.

The first slide illustrates the exposure methods and the materials we used. The exposure methods include inhalation, intratracheal injection, thread transfixion and pellet implantation. The materials we used included the polycyclic aromatic hydrocarbons and some radioisotopes. There were included in the group of chemicals the "standard" ones with which you are all familiar and, which have been of considerable importance in cancer of the skin. The animal species we employed were mice, rats, and rabbits.

The next slide illustrates the exposure chamber technique we used for inhalation study. The actual chamber is inside a negative pressure box for protection of personnel, since we were dealing with aerosols of highly carcinogenic potential, *e.g.*, benzpyrene.

The next slide shows another procedure that we used, one that was devised by Dr. Kuschner of our staff, and which depends on the implantation, in a selected bronchus of a rat or a rabbit, of a pellet which contains the test material. The pellet is fashioned to fit the chosen bronchus, generally a lower segmental one. In the rat shown, the pellet is half a millimeter in diameter and five millimeters long. The pellet is fashioned out of a cylinder of stainless steel mesh and has fine hooks, so that it will be retained in the bronchus. The steel mesh is impregnated with the test material by a procedure suitable to the material in question. The pellet is then placed in a trocar and inserted into the selected bronchus either with or without a fluoroscopy as a guide, and it is released at the proper point where it remains with a high degree of success throughout the life of the animal. Ventilation of that segment of the lung is blocked by the pellet and in the absence of antibiotic treatment there is a tendency for infection to occur. For this reason, antibiotics have to be given to the animal.

The next slide shows an x-ray film of the chest of a rat showing the pellet in place. The pellet lies in the lower segmental bronchus. You can see its shadow just to the left of the vertebral column (indicating).

The next slide shows an intratracheal injection in progress, another dosage technic that was employed.

In the case of the thread transfixion of the lung, the procedure used is to impregnate an ordinary cotton thread with the test material, with or without the use of a binder. This then is pulled through the lung tissue of the rodent. In the case of the mouse, this can be done by parting the walls of the chest cavity and inserting the thread directly into the lung. In the case of a rat, we use artificial respiration and open the thoracic cavity.

The next slide lists the variants that we use in the intratracheal injection procedure. We examined a variety of materials with a variety of adjuvants and according to different series of test patterns. In short, we have yet to observe a bronchogenic cancer from the intratracheal injection of such a highly potent material as methylcholanthrene, in spite of the fact that we have used repeated-dose procedures for even as long as a year.

The next slide illustrates some of our results with the inhalation techniques. The same reservation that I made about intratracheal injection applies here; we have not yet produced brochogenic cancer in any experimental animal by inhalation. We have, on the other hand, observed adenoma production by this procedure. This, as you remember, is the lesion which has a certain spontaneous incidence in most rodents, particularly certain strains of mice. In these experiments, an increase in the number of adenomas was observed.

However, one of the most interesting things in this table is found in the line next to the last, in the last column, in which animals (mice) were exposed to methylcholanthrene. Although they did not show brochogenic cancers, they did, in fact, develop skin cancers. In other words, the mist that they were exposed to was sufficient to drench their skin with enough carcinogen to produce skin cancer; and, although it drenched their lungs also -- because we found it there -- it did not produce lung cancer in those animals.

The next slide shows the positive results we secured in the terms of bronchogenic cancer, with the two other dosing procedures that we employed, namely, the thread and the pellet. These results that I show here are typical and differ with the material used. For example, the methylcholanthrene series showed 4.5 percent carcinoma in mice. Dibenzanthracene treatment showed up to 33 percent. We can now say that we can reproducibly produce a bronchogenic cancer in rodents by the thread implant procedure . This is essentially a confirmation of Andervont's findings, with extension to the rat. The other procedure that I mentioned, involving the pellet use, is also very satisfactory for inducing bronchogenic cancer in rats. Its use in rabbits is less rewarding. Both of these procedures, then, provide at least a means for inducing the kind of cancer seen in man and for which we should have considerable interest.

There is one point of great importance and, it seems to me, one that has to be resolved before we are ready to use any of these procedures in a knowledgeable way for the appraisal of the carcinogenic potential of suspect materials. This is to determine why these two procedures, namely, the thread and the pellet, have been successful, whereas the other two, intratracheal injection and inhalation, have not. In this regard, we are particularly interested in the inhalation procedure since, in most instances, we assume this is the mode of entrance of the carcinogen into the pulmonary system.

The successful techniques differ from the unsuccessful techniques in a variety of ways. The two most striking differences, perhaps, are the fact that the successful ones both use procedures which insure a high degree of persistence of the agents at one site in the pulmonary system, and the successful procedures also differ from the unsuccessful ones in that the former produce some degree of tissue trauma. They involve the introduction of a foreign object. We believe that both factors very probably play roles and we have little doubt that tumors can be produced by intratracheal injection or by inhalation, if we could appropriately meet these two limitations. Whether these have the same importance in man as they do in the rodent, we don't know, but this is one of the things that will have to be resolved before the procedures can be applied in a meaningful way, we believe, to gesting of unknown situations.

The next slide shows the positive outcome of a pellet experiment in a rat in which bronchogenic cancer was induced in the lung. A massive brochogenic tumor is shown at the left of the slide -- with metastases to the kidneys on the right.

The last slide illustrates one of the points I made, namely, that there is a lack of persistence of the agent in the lung after inhalation. These show the rapid disappearance of methylcholanthrene from the lungs occurs in mice which have been placed in a chamber containing methylcholanthrene aerosol for a short period.

The other factor , that dealing with tissue damage, is being examined currently by a variety of ways. We are, for example, exposing our animals to bronchial irritation by several means: sulfur dioxide inhalation, the implantation of "blank" pellets, the insertion of "blank" thread -- that is, threads and pellets not containing carcinogen. These animals are subsequently exposed to aerosols or intratracheal injection of known carcinogenic agents.

DR. GOLDSMITH: I wonder if Dr. Vorwald would care to comment on this paper?

DR. VORWALD: I haven't got much to contribute to Dr. Nelson's paper other than to say that I have been following his work for many years.

Perhaps the most significant thing that I might say is to cite the difficulties attending the production of cancer of the lung in experimental animals. Dr. Nelson brought this out; but I should like to emphasize two points. The first is that the tumors which we are able to produce in experimental animals are too often unlike the tumors which we see in the lung of human subjects. We are striving, of course, to reproduce these so-called human squamous cell carcinoma. The second point is that the techniques must be highly refined in order to bring the test material into the strategic sites of the pulmonary tissue. There are many variables which we must consider in this work, including, the species of the animal, the age of the animal, and also what I call the biological half-life of the substance in the lung.

I think that Dr. Nelson's use of the pellet and of the thread, in addition to imposing a factor of irritation, has also accomplished a longer biological half-life in the lung, and thus enables the potential carcinogen to exert its maximum effect.

DR. FISHER: Is anybody able to report at this time on any progress in the post-infection air pollution carcinogen studies being done at the University of Southern California?

DR. DAVIES: I think I can say that those results are not in yet, Dr. Fisher. These studies produce a virus infection in animals and then follow with carcinogens, or unknown substances suspected to contain carcinogens and thus produce carcinoma.

I would like to say a few things about Dr. Nelson's report. He is to be commended for overcoming many of the difficulties in the problem of developing a bronchogenic carcinoma in animals with foreign substances. So far I think Dr. Vorwald has produced one of the only induced bronchogenic carcinomas, using beryllium. There have also been bronchogenic carcinomas produced with radioactive agents, but not with polycyclic hydrocarbons. Dr. Nelson has demonstrated, I think very well, why a number of people have been unsuccessful in producing epidermoid carcinomas of the lung in animals either with aerosols or with smokes, exhausts, or cigarette smokes.

The closest that anyone has come to this has been Dr. Leuchtenberger at the Western Reserve University who produced pre-cancerous changes with cigarette smoke, changes that would be called, by some at least, carcinoma-in-situ. This was reported a few months ago. But, because of these negative results by so many people, tumor produced by skin application, by subcutaneous injection, or the enhancement of pulmonary adenoma production in susceptible strains of mice has been accepted as evidence for tumorigenicity.

Not knowing whether the production of cancer in the skin is evidence for carcinogenicity in the lung, and not knowing for sure whether enhancement of the frequency of benign tumors in the lung is really evidence for carcinogenicity of the human type, Dr. Nelson made a frontal attack on using a known carcinogen, instead of trying unknowns such as atmospheric pollutants or cigarette smoke. First, he has demonstrated the method and the next step, as he points out, is to try various unknowns.

I would like to ask Dr. Nelson whether he has any explanation for the difference between methylcholanthrene and dibenzanthracene in their relative production of sarcomas and carcinomas. I believe that he said that methylcholanthrene produced 63 percent of sarcomas and only about 4 percent of carcinomas, whereas, dibenzanthracene produced about 15 percent sarcomas and 32 percent carcinomas.

DR. NELSON: I haven't the foggiest notion, Dr. Davies.

DR. GOLDSMITH: Are there comments from the floor?

DR. DAVIES: I would like to make one more statement. In my travels I have picked up the belief that among the polycyclic hydrocarbon carcinogens, at least among those that are strongest and best-known, there doesn't seem to be too much difference in carcinogenicity for one organ or another or for one species or another. They all seem to be able to produce either sarcomas or carcinomas in whatever organ they are tried on, provided that the material reaches the cells which eventually become malignant. I think that this is an extremely important point in the case of the lung. It is probable that the carcinogens have not reached the cells which are potential precursors of becoming malignant cells. In spite of being a mucous membrane, epithelium of the tracheobronchial tree of the lung obviously has extremely good defense mechanisms. It has a sheet or blanket of mucus. It has cilia which carry away that mucus to get rid of it as it holds foreign material. Then it has a surface layer of epithelial cells which are completely differentiated and, therefore, cannot divide and cannot become malignant. So any potential carcinogen to be more than only "potential" has to get through these three layers, to get down to the cells in the basal layer which can actually become cancer cells.

DR. GOLDSMITH: I am interested in your observation because of a point that was made by Dr. Fletcher of England when he visited the West Coast. It was concerning the species differences in the pattern of mucus production.

As I recollect his observations, based on the pathologic studies of Dr. Lynn Reid, the rat has a more abundant mucus gland structure than the mouse, and hence, has a different pattern of mucosal defense, or perhaps really sub-mucosal defense. I wondered if Dr. Nelson would care to comment on any of the species differences that he has observed. I believe you used three species - is that right?

DR. NELSON: That is right. The species differences have not been striking. We have had positive outcome in both the mouse and the rat by the thread and we have had a positive outcome on the rat with the pellet. We have not used the pellet in the mouse since it is not adaptable to that technique. We have had negative results in both species by inhalation and by intratracheal injection. I think these differences you mentioned might very well be relevant.

DR. GOLDSMITH: The next presentation on the panel will be that of Dr. Gilliam, from the National Cancer Institute, who has very kindly consented to present an informal discussion of "The Epidemiologic Method In The Study Of Air Pollution and Cancer In Man." Dr. Hueper will not be here to present his paper.

DR. GILLIAM: The discussions yesterday and today are primarily concerned with laboratory investigation which would not be conducted unless they were thought to have some bearing on the problem in the human population. We have other ways of examining disease in human population through epidemiologic studies. Since the general field of epidemiology is probably not familiar to most of you, it might be worthwhile to give some idea of what the epidemiological method is, and some of the kinds of evidence in human experience which may be related to the problem of atmospheric pollution as it might involve cancer.

Epidemiology is the study of disease in human populations, having for its objective an attempt to characterize the kind of people who acquire disease and the kind of people who escape. In the initial phases of epidemiological investigations the kind of characterizations of the people that are possible are usually of a very crude sort, such as that one age group is more at risk to disease than another age group, or that persons of one race are more at risk than another. As knowledge of the disease progresses, and particularly as there are developments in other sciences, it is possible to apply these other techniques to consider studies of the disease in human population and to refine in greater detail the characteristics which bear on its occurrence.

Epidemiology is a "collective science" in much the same way that clinical medicine is a collective science. Clinical medicine draws on the facts of biochemistry, anatomy, physiology, etc. Although it deals with all of them, and it is no one of them, because it has a different objective than any of them. To characterize the people who acquire and those who escape disease through study of mass phenomena of disease is dependent upon the demonstration that groups with certain characteristics have either a greater or less risk to either acquiring the disease or dying of it. The most useful measure of risk is incidence. Incidence is a measure of the probability that one of a group will develop or die of the disease during a given period of time.

"Incidence" is one of the most misused words of clinical medicine and pathology. You will frequently find, in the same article, as many as four totally different kinds of data all labeled as "incidence," and conclusions drawn from them that would be valid only if the data represented incidence, in fact. Most frequently, data labelled as incidence in the literature are what are known as relative frequencies. For example, there is the evidence bearing on the alleged increase of leukemia in radiologists. These data consist simply of a ratio or a relative frequency. The observation is that among non-radiologist physicians, five-tenths of one percent of all deaths in about a twenty-year period, were attributed to leukemia, while among radiologists four and a half percent of all the deaths during the same period were attributed to leukemia. This is not incidence. It is not the probability of non-radiologist physicians dying of leukemia, or the probability of radiologists dying of leukemia, but it is merely the ratio of leukemia deaths to all deaths, in the two classes of physicians. This ratio is very sensitive to at least two important variables. If other causes of death are low, this ratio has got to be high. The other variable, of course, depends upon the sensitivity of the ratio to differences in age composition of the two groups. The ages, are in fact quite different in thesetwo classes of physicians. It has been concluded, however, that because this ratio is nine times as great, radiologists have nine times the risk to leukemia than do the non-radiologist physicians. It can be very simply shown with these same data that if the risk in radiologists were, in fact, as much as nine times, this ratio would have to be around 12 to 14 percent, instead of four and a half percent. But the point I am trying to make is that those data do not represent incidence. All that can be said of them is that if radiologists were, in fact, at greater risk to leukemia than non-radiologists, a number of other things being equal, you would get some such ratio as that. This is quite different from saying that radiologists have nine times the risk to developleukemia than do non-radiologists. It does justify a hypothesis that radiologists might be at greater risk to leukemia, but does not establish this as fact.

Epidemiological methods of measuring risk to disease may be divided into two general groups - the direct and indirect. The indirect or case history method is the time-honored method of clinicians and pathologists. Here you start with a series of cases, you identify their characteristics, compare them with a control group, and then make estimates of the risk. In the direct or population method, you take a population or group of people, divide them according to their characteristics, and then measure incidence of disease in the groups with different characteristics.

Assuming that you have a study which is technically sound, and that you have demonstrated that a group with certain characteristics has an unequivocally excessive risk to a disease, what does it mean? At the very least, it justifies a hypothesis that the characteristics that you think you are measuring are of causal significance in the natural history of the disease. You may, however, have an increased risk to the disease where the habit, or environment, or the host characteristics bear no relation whatsoever to the disease, in terms of causation. For example, there are at least two unpublished series of data which show that risk to cancer of the lung is about three times as great in men with false teeth as in men without such dentures. Until we have some biological reason for believing that false teeth might be causally associated with this disease, it is silly to believe that there is any causal relationship involved at all. Another example may be drawn from the publications of the British Registrar General, which data have been so useful in giving leads to so-called occupational cancers. In these data there is the demonstration that dock workers have an extraordinarily high risk to syphilis. Now that we know the cause without which syphilis cannot exist, it is perfectly evident that these dock workers are not exposed in their occupation to some specific chemical "syphilogen." This association, which is a substantial one, quite obviously bears no causal relationship either directly or indirectly to the disease at all. There is undoubtedly a reason. The reason escapes us, but there is undoubtedly a reason for it.

I may mention that dock workers also have a very high risk to cancer of the lung. One author at least has said that this is due to the fact that they work in a dusty atmosphere of grain dust polluted with arsenic, and that therefore in their occupation they are exposed to a specific chemical lung carcinogen which causes the disease. This is a justifiable hypothesis, but with a similar and actually much greater excess of syphilis than of lung cancer, it is certainly not due to occupation exposure to a specific chemical "syphilogen."

On the other hand, while in some instances an increased risk may not mean cause in any sense of the word, it frequently does mean that this occupation, this habit, or this environment -- this host characteristic -- is causally related to the disease. Drawing an analogy from other diseases of known cause I can think of at least three ways in which risk may be causal. One, it may cause the disease in the very specific sense that a Type III pneumococcus causes lobar pneumonia. And this is the way in which workers in the cancer field speak of causal relationships. They generally mean that cigarette smoke causes lung cancer in the sense that a Type IV pneumococcus causes lobar pneumonia. Exposure to the dusty atmosphere met with in processing chromate ores, they say, causes lung cancer in the specific sense that a Type VIII pneumococcus will cause lobar pneumonia. Or working in the radioactive mines of Schneeberg would cause it, in the specific sense that a Type III pneumococcus causes lobar pneumonia. As you know there are some 30 specific pneumococci which will cause lobar pneumonia. In the cancer field when people speak of cause, they generally mean cause in that specific sense.

There is a wealth of experimental evidence, including the kind of evidence which Dr. Nelson just presented, which supports that feeling, that there are many specific causes of cancer. An increased risk, however, may mean cause at least in another sense; that is, cause in the sense that a diet, the main staple of which is corn, or the main staple of which is alcohol, causes pellagra. At the turn of the century in the three major pellagra areas in the world, the risk to pellagra was extraordinarily excessive in people whose main staple of diet was corn. Further, it is the common experience of large city hospitals that pellagra is now virtually limited to people whose main staple of diet is alcohol. These are causes in a very real sense; but they are also causes in the sense that elimination of corn or alcohol from the diet, would not prevent a single case, unless in the course of eliminating those factors a food with the pellagra-preventive factor was substituted. There is a third sense in which associations might mean "cause." That is "cause" in the sense that poor nutrition causes tuberculosis. There is little doubt that the ultimate course of infection with the tubercular bacillus is governed partially by nutrition. But this disease cannot occur without the bacillus. There may be other ways in which increased risk in some group with certain characteristics might reflect cause. These are the three that occur to me.

The evidence in human experience bearing on air pollution in cancer, I think, might be usefully grouped in three general classes. One is the evidence that people who pollute their own personal air very heavily, such as cigarette smokers, do unquestionably have a very high risk to cancer of the lung. It is presently not known if this is a closed relationship, or if it is, in which sense mentioned above, it might be causal. There is a second type of evidence which bears on men employed in certain occupations where they are exposed to a variety of agents in more concentration than for the general population. It is quite clear that men in certain occupations have excessive risk to various cancers, including cancer of the lung. Again, it is not known whether or not most of these relationships are causal. The evidence with regard to occupational exposure itself, however, might be broken down into several groups. The bulk of it unfortunately is relative frequency evidence, which should initially be looked upon largely in the same light as clinical impression -- as a lead for further investigation. There are, however, a number of employee situations where risk has very definitely been demonstrated as excessive. These are such as chromate workers, asbestos workers, men who suffered mustard gas poisoning, etc. The third general type of evidence is the observed rural-urban difference in disease. There have been some studies which strongly suggested, or were strongly consistent with the idea, that atmospheric pollution bears some significant relationship to this difference.

These, then, are the general methods of study of disease in human population, where the effort is to show whether or not risk is modified with certain characteristics. But once an excessive risk is demonstrated, it becomes necessary to set up a hypothesis and test it for its consistency with all the facts of the disease in humans, plus all the facts of the experimental production of the disease in animals.

DR. GOLDSMITH: Dr. Davies, would you care to start the discussion?

DR. DAVIES: I think Dr. Gilliam has brought out some very important points. I would like to discuss the last point that he made, about the various types of air pollution.

If we look at just the one type of cancer, the lung cancer, resulting from air pollution, and consider its frequency in terms of urban and rural differences, it immediately becomes obvious that you can get into trouble by not taking into consideration that the other two factors which Dr. Gilliam mentioned, occupational history and smoking history. Up to the present the evidence has been gathered for smokers, or for occupations, or for urban-rural differences, each independently of the other. There have been studies, such as one in England, in which urban-rural differences and smoking patterns were compared; but, the only study of this sort which is being conducted in this country, in which consideration is given to smoking habits, occupational histories, and the residential histories of the individuals concerned, is that of Lester Breslow.

So, I think I can say this without a fear of contradiction. Even though the epidemiological evidence that smoking is a causative factor in, or is statistically associated with, lung cancer, is greater than such evidence regarding urban-rural differences, it does not mean that smoking causes more lung cancer than air pollution in cities. We don't know the quantitative aspects of the problem. It may be that smoking does account for 85 or 90 percent of lung cancers. It may be that it accounts for only 40percent. I don't know and I don't think anyone else does. I think that most of the controversy that has raged over the country has been at a "quantitative level," rather than one of "either/or." We should not think in terms of "either/or," but should now get down to the point where we try to quantitate how much of this lung cancer is due to one factor and how much due to another.

DR. GOLDSMITH: I would like to ask Dr. Mancuso to comment briefly on his observations concerning the epidemiology of lung cancer, or to raise any questions concerning Dr. Gilliam's paper.

DR. MANCUSO: I believe Dr. Gilliam established the basic principles relative to the epidemiology of air pollution. I think I might add a little bit to it in the sense that perhaps the others are unaware of the complex nature of the chemicals in industry for which we have very little information concerning toxicological effects.

In the epidemiological approach we lack certain basic reference data which is being collected at the present time in regard to urban-rural differences. I think that one mistake that may be made in epidemiological approaches is to attempt to define a particular study which will provide the over-all answer. I do not think that is necessarily true in epidemiology, as it would be in a laboratory study, because of the variables associated with human experience.

The urban-rural differences for certain cancer sites are very significant, and rarely do I hear anyone mention anything about cancer of the esophagus. Yet the urban-rural difference is greater for cancer of the esophagus than it is for cancer of the lung. There are other cancer sites which show a marked urban-rural gradient.

I think in the epidemiological approach that we must also consider studies of families, husbands and wives, from the point of view of exposure within the same environment and diet. There are so many variables among humans for which we should have undertaken epidemiological studies long ago. We have to "backtrack" now and conduct these basic epidemiological studies to determine what diseases are related to what populations, and to what population subgroups.

Until we collect this basic data, we will be unable to refine the epidemiological data further to determine what relationship exists with occupation, and so forth. One approach, of course, is to go back to the occupational environment and select those environments where the population subgroups are exposed to a single chemical. You would have to find such a situation, and then conduct cohort studies of these populations exposed to a single chemical, or single type of process, and determine the death pattern of this particular industry group. It is by studying death patterns of these various industry groups that we can determine what other organs may be affected. At the present time we are without knowledge concerning the effect on the individuals of low exposures over long periods of time.

While at the present time the fad is to study lung cancer, because of its marked incidence, there are undoubtedly other types of disease that may be occurring and to which we are not giving appropriate attention. It is possible, I believe, to conduct cohort studies of industry groups, and then from this go back and try to add this particular information to a community where this type of industry may be located, and gradually add from one chemical or process to two, and so on, and build up in that way.

DR. GOLDSMITH: I wonder if there are any other comments from the floor. There are none.

Dr. Heimann, would you mention briefly the progress being made on the nation-wide study of carcinogenic substances obtained from the high volume sampling network?

**DR. HEIMANN:** This discussion was to be presented by Dr. Hueper. I shall try to give you a few of the highlights that I happen to know about on the study that is being done by Drs. Hueper and Kotin with material supplied by the Community Air Pollution Program of the Robert A. Taft Sanitary Engineering Center.

Drs. Hueper and Kotin are studying the effect of specific portions of particulate samples that are being collected by the RATSEC as part of its over-all study of particulate loading in cities throughout the United States. For eight cities, for which the data for cancer frequency has been gathered, the epidemiologic data indicates that there are wide differences. For these same eight cities particulate samples are being collected, broken down into their components, and these are being examined for their carcinogenicity. The cities are: Los Angeles, San Francisco, Atlanta, New Orleans, Cincinnati, Detroit, Birmingham, and Philadelphia.

The samples are broken down in such a way that Dr. Hueper obtains enough of the aromatic organic compounds for study. Dr. Kotin is receiving two sets of samples: the aliphatic fraction and the oxy-neutral fraction. They are using two strains of mice. One strain is highly susceptible to cancer and the other strain is highly resistant to cancer.

The objective of the study is well stated in the last paragraph of Dr. Hueper's abstract. He states, that it is hoped that this kind of information which they will gather will assist in supporting the suggestive data which exist on an epidemiologic basis for these communities. It will provide just one extra link in the chain of evidence as to whether or not there are substances in the air that are contributing to the lung cancer problem in these communities.

We recognize that the study is limited to the solid particulates and this limits its value.

The material is handled so that it is quite fresh when it arrives, and it is treated so that very little oxidation can occur in it before it is properly divided for distribution to Drs. Kotin and Hueper.

Dr. Hueper is doing this work with National Cancer Institute intramural funds. Dr. Kotin, at this time, is working with the assistance of some funds from the Public Health Service.

DR. GOLDSMITH: May I ask a question? It seems to me, in light of the fairly striking data that was presented by Dr. Nelson concerning the possibility of inducing pulmonary cancer, which strongly resembles bronchogenic carcinoma in its site and pathology, would it not be prudent, Dr. Heimann, to take some of the material obtained from the samples, assay it according to the methods Dr. Nelson has indicated are capable of leading to positive results with known carcinogens? In other words, would this not add to the specificity of the study?

DR. HEIMANN: We would support such work, if Dr. Nelson would like to have some of the material.

DR. NELSON: I think it might be of considerable interest. We are not ready to go into unknowns yet. I tried to make this clear. I think we have many points in regard to mechanism to clear up first. But we are ready to begin in a small way on materials that we have strong reason to suspect.

DR. HEIMANN: In the Air Pollution Medical Program of the Public Health Service we believe that the basic source of information on what to do about studying carcinogenicity of air pollutants rightly lodges with the National Cancer Institute. The first program that was suggested by the National Cancer Institute was the one that I described. If there are others that people would like to suggest, we would be happy to take this up with the National Cancer Institute to see if we could get support in one way or another for this work.

DR. GAST: Dr. Heimann, wasn't there also a question raised by Dr. Hueper about the chemical analyses of the samples?

DR. HEIMANN: Yes sir.

DR. GAST: He requested, I believe, that some effort be made to demonstrate the kind and amount of polycyclic materials that might be present.

DR. HEIMANN: Dr. Hueper asked that when these samples were provided to him and to Dr. Kotin, he (Hueper) be informed of the degree of radioactivity of the samples, and also of their 3, 4-benzpyrene content. The radioactivity data have been provided to him. However, to find out how much 3, 4-benzpyrene is present in the samples, I understand, is a much more difficult procedure than had been anticipated by the chemists. This program started July 1 of last year, 1957. It is expected that by July 1 of 1958, which will be the beginning of the second year of this work, the chemists at the RATSEC will be able to provide these data of how much 3, 4-benzpyrene is in any given sample. The study requires test materials for two years. In the third year the animals are continued to be observed. The whole study is expected to take about three years.

DR. GOLDSMITH: Is that three years for a given sample? Is that three years' observation of a given animal, for a given sample?

DR. HEIMANN: For some it will be that; but, for others it will be for a shorter period of time.

DR. GOLDSMITH: I wonder if there are any other questions?

DR. DAVIES: I don't have the picture clear about the way the substance is applied. Is it collected for one week or one month, and then applied? As I understand it, there is some seasonal variation in atmospheric pollutions, in quantity and quality. Will this all be smoothed out or will there be any adjustment made for the interval of time over which the substances are applied to animals? In other words, it might be six months during the summer that the sample would be collected from New York, and Chicago might be the winter six months, or something of that sort.

DR. HEIMANN: The samples are collected during any one month. This may take one day or a week, or longer, for the collection. But, what has to be done is that a long enough period is used so that a sufficient quantity is available for the chemists to break down into its component parts.

DR. FISHER: From each city every month's material is collected and sent to Drs. Kotin and Hueper.

DR. NELSON: Dr. Goldsmith, I wonder if I could comment on the experimental pattern of such assays:

The normal developmental pattern for tumors of this sort shows a reasonably slow induction time, or long latent period. We also know, from quite a body of experimental work, that if you continue to dose in a repetitive manner, the differing doses at differing times in the life cycle of the animal are of different effectiveness. Some are more efficient than others. We can't specify in detail what they are; but, in general the later doses are somewhat less effective than the earlier doses. It is to be expected that, for example, in a place like Nashville, there will be a seasonal variation in carcinogenic potencies, and it is possible that collection and dosage might be so synchronized that the potent samples might be given in the resistant phase of the experiment. So there ought to be some way of pooling these materials to take account of these seasonal variations.

DR. GOLDSMITH: Thank you very much, Dr. Nelson. Are there other questions or comments?

If not, in closing, I would like to mention two cancer projects which are being actively undertaken by my colleagues in California. Dr. Dunne is in charge of a prospective study of both occupational groups and population groups, the second being based on the roster of the American Legion and which includes about 71,000 Legionnaires and 49,000 of their spouses.

The second group, which is fairly busily engaged in laboratory methods for detection and isolation of potential carcinogens is under Dr. Harold Helwig. They are working very vigorously at various fluorescent screening techniques. I would be glad to discuss with anyone what I know about these studies.

DR. HEIMANN: Thank you very much, Dr. Goldsmith. We will proceed now to the next panel, "Allergy And Air Pollution." Dr. Whittenberger has agreed to be chairman of this panel.

## PANEL VI

## AIR POLLUTION AND ALLERGY

DR. WHITTENBERGER: The presentation on the "Studies Of Pollens As Air Pollutants, A Preliminary Report", will be given by Dr. Wendell Hewson.

DR. HEWSON: Our study at the University of Michigan is an interdisciplinary one involving research by a team consisting of: 1) botanists, for analysis of the production and release of ragweed pollen at the source, under Professor W. H. Wagner, Jr.; 2) meteorologists, to consider atmospheric transport and diffusion which I am directing; 3) allergists, for the study of the allergic response of individuals, and related problems, under the direction of Dr. John Sheldon; and 4) public health statisticians, on experimental design and data analysis, under Professor F. M. Hemphill. Our studies are too broad and complex to be considered in detail at this time. One fact that I shall stress is that these natural pollutants are increased by man's activities.

First, we will consider briefly the botanical phases. The main varieties of ragweed plant studied are *Ambrosia trifida* (the tall or giant ragweed), *Ambrosia artemisiifolia* (the low or common ragweed), *Ambrosia psilostachya* (western or perennial ragweed), *Ambrosia coronopifolia* (eastern perennial), and a new hybrid perennial, *Ambrosia intergradiens*, which our investigation has disclosed. We have charted these plants as to the relative frequency of occurrence in Michigan, normal height, the number of chromosomes in different types, and the pollen diameters which range from 14 microns to 26 microns. This new ragweed, *Ambrosia intergradiens*, represents a cross between the perennial *Ambrosia coronopifolia* and the annual *Ambrosia artemisiifolia*. There are definite indications of an eastward migration of this new ragweed. This fact has, I think, very important long-term public health implications.

The perennial *A. coronopifolia* is distributed through the western and northern portions of Michigan, in 42 counties. The new *Ambrosia intergradiens* is less extensive in its distribution. It is found only in the northwestern portions of Michigan, in 12 counties. Median leaf sizes for these three types of ragweed have been determined. There are interesting differences among the ragweed types which are significant botanically and perhaps medically.

I shall now go on to a brief mention of meteorological factors. Many of our studies have been made at the Jackson Prison. At the general site of our studies on the prison farm there is a 100-foot tower with instruments located at 4, 12, 25, 50 and 100 foot elevations. At each of four levels there is an anemometer, a wind vane, a temperature element, and finally a 6-head sampling unit, which gives automotic volumetric sampling for six 4-hour intervals during a 24-hour period, using millipore filters.

Nearby we conduct pre-season experiments, using a plot of ragweed in a field of tomatoes. The ragweed -- 3056 plants in 1957 -- has been grown pre-seasonally, first in the greenhouse and later in cold frames, then brought to pollination in June by manipulation of the photoperiod. This is probably the only ragweed in the midwest that is emitting pollen to the air at that time, so that we do not have a "tagging" problem. Slides for sampling the deposition of pollen are arranged in concentric circles at 20, 40, 60, 80, 160, and 320 feet from the patch of ragweed. The slides are 90 in number and mounted 2 feet above ground. They are changed six times daily, every four hours. Slides are also located in the ragweed patch itself, 4 units on the ground and 4 others at 2-foot heights. In all, we have some 6,000 slides to count.

From preliminary results, we find that one weather influence is pronounced. Cloudy weather appears to have the effect of reducing pollen emission for the remainder of the day. It was found that the drop-off of pollen emission is very pronounced during the early morning hours if cloudy weather develops, after sunrise. We have, in addition, made measurements during the regular pollen season, but those are so complex that I cannot cover them at this time.

Let us consider the medical phase next. The studies of hay fever and asthma on inmates at the Jackson Prison involved 13 selected subjects in 1955 and 11 subjects in 1956; 3 volunteered to stay continuously for a period of three or four weeks in a single group of three rooms (a cell block in the Prison). Very detailed studies of their allergic response, comprehensive pulmonary function tests, and pollen concentration measurements in the cell block were made. In 1957 there was a follow-up study to elucidate some of the points that were not clear from the earlier two years. Laboratory analyses included blood eosinophil counts and nasal smear examination for eosinophils. The pulmonary function studies consisted of one-second and total vital capacity, maximum breathing capacity, and maximum expiratory flow rate. Record was kept of hay fever and asthma (objective and subjective) symptoms in addition to pollen counts, both by gravity slide and by volumetric methods.

Our results show that even with selected and controlled groups of subjects there are serious complicating factors. The early or minimal changes that we had expected to find have not shown up as clearly as we had hoped. A new technique, using a nitrogen gas analyzer of expired air, may be more rewarding. Nitrogen gas studies were made in 1957, but the information is not yet fully analyzed.

As the patient's hay fever or asthma increases, all laboratory studies become significant. There are exceptions, but no threshhold values for reactions have as yet appeared. The symptomatology follows the general pollen concentrations, except that in the morning, increases in hay fever symptoms precede increases in pollen concentration. Meteorological factors may be important, but the analysis of these is not complete.

The second line of attack on this problem is through the test chamber which is now in the process of construction. It will be a chamber for human occupancy in which we hope to obtain definitive values of threshold concentrations of exposure. In this chamber pollen concentration, temperature and humidity will all be controlled. A second main study is that of the antigenicity of the tapetal fluid in the anther of the plant. There is definite evidence that this fluid is antigenic in nature and further studies are planned. A third study is in regard to localization in the plant cell of the ragweed antigen. Rough separation has been made of the intine and exine pollen, and passive transfer neutralization tests of the fractions made on three recipients. These studies suggest that the protoplasm of the pollen contains the antigenic material. The fourth phase is concerned with pollen recovery from respiratory tissues. Initial studies were made on guinea pigs. The primary question is: Are ragweed pollen found in the lungs, for example, in the alveoli? There is some evidence that these

20-micron pollen particles do get down as far as the alveoli. This conclusion is based on analyses of human lung tissue obtained in six autopsies on persons who died in the ragweed season. It is interesting that much more pollen was found than would be expected from information of the amount of ragweed we believe to be present in the air.

All three phases of the research, botanical, meteorological, and medical, are coordinated with the guidance of public health statisticians, who advise on experimental design and data analysis.

DR. WHITTENBERGER: When you called attention to the fact that man has increased the concentration of natural pollutants, were you referring to this new hybrid ragweed?

DR. HEWSON: Not specifically. Ragweed thrives on ground that has been newly disturbed. With all the clearing of land, the building activity, and suburban developments that are going on in the areas where ragweed may develop, there is evidence that the plant is increasing in numbers and also migrating.

DR. MENEELY: I have an impression that when pollen actually gets on a moist surface it behaves as though it were confused, as if it had landed on a plant. Does it not then proceed to expand and actually to inject protein material into the moist surface?

DR. HEWSON: I believe some such process may occur. Whether this happens on all mucosal surfaces, or whether there are certain specific surfaces in which this happens, I do not know. This is a question I think the botanists might answer.

DR. MENEELY: I brought the point up because, so far as I know, it is the only air pollutant that actually "gets in and fights." It is an *active* agent.

DR. HAYES: What evidence do you have that the species *A. intergradiens* is a hybrid?

DR. HEWSON: Chromosome studies indicate that it is a cross between the perennial *Ambrosia coronopifolia* and the annual *Ambrosia artemisiifolia.*

DR. HAYES: But it does not seem to be a polyploid.

DR. HEWSON: It is a triploid, which is excellent evidence of its hybridity.

DR. VORWALD: Are you making studies of the adsorption or absorption characteristics of pollen, as to how they might respond to organic and inorganic compounds in the atmosphere?

DR. HEWSON: No. We have not done that so far.

DR. FREDRICK: Apropos of this matter of effect of ragweed pollen on health. We have explored this problem of the concentration of the ragweed pollen in the air during the pollen season over a period of three or four years. We also have tried to see what relationship the air-borne pollen level might have to the general health situation. In doing this we ran into a very exasperating situation in Detroit that one may find in other areas. This was that our first fall "colds", the first wave of upper respiratory infectious disease that sweeps through our population, just about conincides with the pollen season. Perhaps if we went through several years we might be able to find one lucky year when the onset of the first wave of fall respiratory disease would come a little too late to coincide with the ragweed season. We have really had a problem in this regard, and we haven't made much headway.

DR. HEWSON: Are you sure they are not related?

DR. FREDRICK: I am not.

DR. HEWSON: Atmospheric transport is very important in the entire problem. Our evidence shows that a very large proportion of the pollen emitted from a given plot comes to earth again within a distance of a few yards from the source. Dr. P. H. Gregory, in England, for example, makes the statement that under normal conditions of turbulence 99.9 percent of the spores liberated near the ground come to earth within a hundred meters of the source. The bearing of this on our problem is that ragweed grows along highways a good deal. Everybody is on wheels. With the delayed allergic reactions that may occur, one serious question is: Do our people receive very high loads of pollen from roadside ragweed in going to work? The morning is also the time of maximum emission of ragweed pollen. Perhaps passing cars continue to raise clouds of previously grounded pollens. Thus, it may be that pollen concentrations measured on our buildings, for example, as in the center of the city, may not be truly representative of those concentrations that cause symptoms. Perhaps studies in the Seattle area, for example, where ragweed is practically non-existent, and comparison with other areas where weather types are somewhat similar and ragweed is also plentiful, might give some information on the point raised by Dr. Fredrick.

DR. WHITTENBERGER: The second report in this section is by Dr. Scheel on "Immunochemical Changes Associated With The Inhalation Of Respiratory Irritants."

DR. SCHEEL: We reported a year ago that we observed a precipitin reaction in rabbits exposed to ozone. In the first place, let's step back one step further and just explore fundamentally what we are talking about in terms of this type of reaction.

In order to get a precipitin reaction, which is a combination of a protein molecule in the serum from an animal with another substance to form an insoluble substance, there is involved something which immunologists have recognized as having a certain degree of specificity. This specificity has been the basis of the biochemical concept that protein synthesis in the body proceeds by a "template" type of mechanism. There is now present in biochemical literature enough evidence to indicate that this probably is true, and that the antibody is produced as a result of a "template" mechanism. The production of an antibody by the body requires one part, i.e., the exposure of the body to something foreign to it. For years, this has been called an antigen. The antigen has always been implied as being exogenous in origin. What I am discussing this morning involves a step in the mechanism of the reaction in the body, which deviates from this idea a little bit, but not too far.

We have a very simple mechanism, a foreign protein activating, a template mechanism in the part of the body which produces an antibody, which then can react with the protein, known as the antigen. This is the mechanism we have used here to identify the first chemical reaction of ozone with the body. Implications are present, and we share your interested speculation on these implications but we do not yet know what the final result of this early work will be.

We have taken egg albumin as a typical protein. It produces the characteristic absorption curve for egg albumin which is known to be principally due to the tyrosine content of the egg albumin molecule. If we expose this egg albumin to about one milliequivalent of ozone for each milliequivalent of albumin, we change the absorption spectrum. We have not necessarily changed the tyrosine content. Nor have we altered the basic egg albumin structure, other than to increase the amount of light that is absorbed. Since this absorption spectrum is principally due to tyrosine, we then took a tyrosine solution to see what ozone would do to that. The tyrosine absorption was apparent in the range of around 240-250.

The next step was with one milliequivalent of ozone, and the third step with two milliequivalents of ozone. To me this means only that because the light is absorbed in regular intervals with greater intensity, we have here a rather simple chemical reaction. When you increase the amount of ozone by twice as much, you increase the amount of light absorption by twice as much. We had similar curves with egg albumin. This type of reaction means that we have a chemical reaction which alters the structure to increase the light absorption.

How do we prove that the albumin truly has native and/or denatured characteristics? Egg albumin happens to be one of those peculiar proteins which, in the denatured form, has an entirely different antibody production (response) than in the native form. If you cook egg albumin and inject this cooked solution into the rabbit, you get a different type of antibody than if the albumin had not been cooked before injection. I would like to emphasize the point here that these have been called denatured proteins because they have been cooked. Their solubility is different. They have different physical and structural characteristics. In this case the albumin made, together with the antibodies in the serum, a very nice reagent for identification of a structural change which may result from a very random reaction, such as we have when egg albumin is exposed to ozone. In addition to the ozone results we also produced a carbon disulphide treated egg albumin.

Our immunization of the rabbits with native egg albumin resulted in a very nice precipitin titer in the animal's serum. Our antigen concentration was 15-thousandths percent protein. In these rabbits the immunization at this time was specific. With heat-denatured egg albumin injected into the rabbit we also had a specific immunization. Our titer was a little bit higher, probably because the heat-denatured egg albumin is in very fine particulate suspension, and a precipitate forms more readily than with the native albumin solution.

With ozonized egg albumin we had a 1 to 4 reaction with the native-immunized rabbit; and, this was considered a non-specific reaction. It has no part to play with the native antibodies created in this rabbit, as will be shown later. With the denatured albumin we had a very nice precipitin reaction, indicating that the ozonized egg albumin was principally a denatured protein. This reaction with heat-denatured antibodies in terms of reaction characteristics, means to me only that there are enough similarities to indicate that the ozonized egg albumin can react with heat-denatured antibodies. However, ozonized egg albumin may have other characteristics, as we shall see later.

In the case of the carbon disulphide egg albumin antigen, we had still principally a native form of antigen or protein. Carbon disulphide is known to react with free amino groups in protein molecules; and, in reacting with only the free amino groups, we would not expect it to alter the linkages which determine the structure of the protein. Here again we had a little denatured reaction. This may be due to the fact that when we made our antigen, the carbon disulphide was put in with the egg albumin in liquid form and we may have obtained a little surface denaturation from the action of carbon disulphide around the surface of the droplets. This we are still exploring. As I say, I don't know what it means. On the other hand, the ozonized egg albumin is principally denatured and also is quite insoluble at the isoelectric point of egg albumin. This bears out the denatured characteristics.

So far we have not said anything about cross-reaction of species. All of these reactions have been due to egg albumin injected into rabbits followed by testing those antibodies with the egg albumin derivative. In this particular experiment which we carried out in two steps on four animals each, we are now considering further steps.

For many years in immunochemistry there has been an idea that haptens, or foreign groups, introduced into a protein molecule can determine the nature of the immunological reaction. This has been demonstrated with cyanates, phenylisocyanates, the iodine derivatives, and so forth. Our current work is akin to this. We started with a group of eight rabbits which, before exposure, were negative to native albumin, and to heat -denatured egg albumin. With ozonized egg albumin their serum gave a "positive" reaction in a 1 to 2 to 1 to 4 dilution. Since these rabbits had never been immunized with egg albumin, it proves that the 1 to 4 reaction had nothing to do with the native egg albumin antibody titer. Never having immunized these animals to egg albumin we exposed them to ozone. Now we again tested their serum. In the case of the native albumin, there was no reaction. In the case of heat-denatured egg albumin, we had a moderate reaction.

| | PRECIPITIN TITERS | |
|---|---|---|
| 8 rabbits | Before Exposure | After Exposure |
| Egg Albumin | - (1/0) | - (1/0) |
| Heat Denatured Egg Albumin | - (1/0) | + (1/32 to 1/64) |
| Ozonized Egg Albumin | + (1/2 to 1/4) | + (1/256 to 1/512) |

With ozonized egg albumin, we found that whatever happened to the rabbit during his exposure had increased the titer to a rather high level, in terms of cross-reaction with ozonized egg albumin.

Now a little bit about the question of how this titer increases. In other words, another characteristic of an immunization process is that the reaction proceeds step-wise. The first exposure gives you a little. The second exposure will give you more. And so on, as you keep up your injections. In the first three weeks of this experiment, the results were not only confusing but rather discouraging, because with a single exposure in mice and rats, we had been able to transform a normally susceptible animal into a tolerant animal. In this case, as a demonstration, we are talking about circulating antibodies in the blood, not about cellular sensitivity. It took about three weeks of one exposure a week to give consistent results. Occasionally, we would obtain a positive one along about the sixth or the seventh day. This was all that kept us going. Around the fourth week, we began to get consistent low titers, which then began to increase until you have the values that I have presented to you.

This means to me that we have, as a result of exposing an animal to this gas, an immunization process taking place in the animal body.

CAPTAIN BABIONE: My questions would deal with the hint that you gave us that perhaps there are in smog reactions, not only circulating or serum antibodies, but cellular antibodies and cellular reactions also. In order to simplify, and try to carry away from here some generalization, which we can all remember, I would like to cross-fertilize this discussion with knowledge that comes from cutaneous sensitivity reactions, and other immunological reactions involving serum, where the sensitizer is a simple chemical that we know is not in itself allergenic.

The chemical (we mark as "S"), as the sensitizer, is itself not an antigen at all; but, when it is combined with protein it may become a complex that is capable of causing sensitivity. This is common in drug reactions, and with many other chemicals in which the complex form is a sensitizer, but the chemical itself may be very simple.

The nitrophenols or the nitrotoluenes, and others in that group, are sensitizers in this sense. By themselves they are inert; but, once they are complexed with serum or with an intercellular protein they are potential sensitizers.

I think what Dr. Scheel has come across here is very interesting. He does not make a combination of protein and ozone, but rather, you may call it altered protein - almost like heat-denaturation of egg albumin. When inhaled ozone comes in contact with the rabbit serum, it changes the albumin in the rabbit serum so it becomes a sensitizer. I think Dr. Scheel demonstrated this build-up of antibodies to the altered serum protein of a rabbit, antibodies that react to another similar antigen, denatured egg albumin. So much for the circulating antibodies, which is all Dr. Scheel looked into.

I would like to throw out for the group's consideration some thoughts about cellular sensitization, which may also enter into the problem of long-range asthmas, as a possible result of chemical pollution of the air. Yokohama asthma might be such a problem. Clinicians frequently are very careless when they talk about "asthma". Anything that wheezes may be called "asthma." Maybe it is just moisture secretion or a thickening of the mucosa, and not really an allergic kind of reaction at all. But, it may be called asthma.

However, let us think, especially in connection with Dr. Carey's presentation, of the possibility that may exist -- this is pure speculation -- of a protein sensitization that is intracellular. If the sensitizer happens to be a chemical which penetrates through the serum without reacting with the serum, and gets into a cell; or, if it penetrates the cell of the lining of the bronchus, it may get through and into the cell before it has a chance to react, and then it forms a complex with the intracellular protein. We know that this happens in delayed hypersensitivity of all types in the skin. Dr. Herman Eisen has shown that those chemicals which are good penetrants, and slow at forming protein complexes, are more likely to cause the delayed reactions, i.e., the intracellular sensitivity reactions. The skin tuberculin reactions and almost all of skin hypersensitivities that develop after sensitization to chemicals are of this type. Industrial dermatologists are well familiar with this phenomenon.

My question would be addressed to Dr. Carey. Does the five-day incubation, that he noticed in Cincinnati, possibly indicate that some of the asthma reactions were due to intracellular hypersensitivity rather than serum or circulating antibody hypersensitivity?

Finally, we talked about hyposensitization, eventually becoming tolerant to ozone. Hyposensitization occurs in industrial dermatitis also. If you have a very prolonged exposure to chemicals, eventually, there is a process of hardening recognized by some, if not all, industrial medical men. So strong is this concept that people who work with cashew nut oil, after six or eight months, may go around with their clothing saturated with the oil; and, although this is a strong sensitizer, it causes no reaction at all in the person who has gone through a phase of acute hypersensitivity and keeps working with it. Eventually he becomes non-reactive. Possibly your ozone hyposensitization might have such a nature as that.

Anyone who goes into describing reactions to smog will have to differentiate the direct irritant effect from the hypersensitivity reactions. I think the nitro-olefins must produce a direct irritant effect, because practically everyone reacts as soon as he enters a tunnel full of automobiles. That is not like hypersensitivity which is limited to a select few. The reaction to nitro-olefins also comes on after a few seconds, which, again, means that it is probably not hypersensitivity.

Smog can certainly cause congestion of the lungs and many things that might be mistaken for asthmas. However, the type of soluble complex that forms in serum could cause the anaphylactic type of asthma, and the type of sensitizer which is able to penetrate within a cell, and cause sensitivity there, would cause a delayed type of hypersensitivity reaction. This is sheer speculation, but some day we may find that one or both of these chemical sensitizations is involved in air-pollution asthmas.

DR. GAST: I have a few questions on the chemistry of the formation of this antigen. In the first place, this is such a tempting and fascinating hypothesis that I think we would want to scrutinize the mechanism a little more closely. This is a glycoprotein -- as near as I can tell -- which means that rather than placing all the emphasis with the tyrosine groups, there are other groupings. There is also hydrogen-bonding. Sulfhydryl-bonding could account for the denaturation.

Secondly, with respect to the curves that you showed, Dr. Scheel, the absorption could very easily be explained by agglomeration of the particles. Did you have any independent measurements of protein content -- such as total nitrogen -- on the materials which had been ozonized and in which you showed a decreased light absorption?

Thirdly, did I understand you to say that the ozone exposure was one milliequivalent per liter?

DR. SCHEEL: This was one milliequivalent to the egg albumin put in.

DR. GAST: To the solution of egg albumin?

DR. SCHEEL: Solution of egg albumin, yes. Now, to get back to your first question. I did hurry over the chemistry rather hurriedly. The egg albumin solutions made up were tested by Kjeldahl for nitrogen content after ozonization, and the reaction is such that a pH of eight and a half the albumin is not insoluble. It remains soluble, so there is no precipitation. If ozonized protein is adjusted to about a pH of four and a half, it precipitates, and this is almost quantitative. The amount of reaction is proportionate to the ozone added to the egg albumin. In order to get a complete job on this we have to add about 3 to 4 milliequivalents of ozone to the egg albumin.

The shift in spectrum in this study is very similar to the shift in spectrum for phenols in their different ionization states. This work was done by two different people about twenty years apart. The last was done in 1936, and I believe it would be of value to do the work again on ionization of phenol. The fact that it occurs principally in the part of the spectrum which in egg albumin is attributable to the tyrosine content, indicated to me that tyrosine may have been the place where the ozone chose to react with the egg albumin. We are not sure whether ozone actually takes part in the reaction, or whether it only unhooks the hydrogen-bonding of the tyrosine molecules. It is known there are 14 tyrosine-residues in egg albumin, and that two of these are normally free. The other 12 are hydrogen-bonded. Whether this actually is an uncoupling of hydrogen-bonding, or not, we do not know at the present time.

**DR. GAST:** Did you do turbidity measurements at the same time? I am talking about the ozonized egg albumin compared to the normal egg albumin. Your decrease at 275 would account for the so-called tyrosine changing, because you have simply agglomerated the molecules.

**DR. SCHEEL:** Well, the solutions were as clear when we finished the reaction, as they were when we started reaction. There was nothing in the centerfuge. There was no indication of precipitation at pH of eight and a half.

**DR. GAST:** How do you account for the decreased transmittance at 275?

**DR. SCHEEL:** The decreased transmittance at 275 corresponds to the degree of ionization of the tyrosine groups, and this is also true of phenol. If you take basic phenols and adjust the pH, so that you increase the ionization of the phenolic group you also decrease your transmittance. This shift in absorption of egg albumin that is denatured by alkaline denaturation, by just taking the pH up to 13, will give you the same shift. In other words, all you have done is to hydrolyze the hydrogen-bonded tyrosine groups. The work by Cramer and Neuberger is very beautiful, and they obtained very similar spectral shifts, as we have shown here.

**DR. GOLDSMITH:** I would like to ask Dr. Scheel, if you have been able to use this test to detect exposure to ozone in humans?

**DR. SCHEEL:** No.

**DR. NELSON:** I have two questions: What was the concentration of ozone to which the rabbits were exposed for the serum precipitin reaction? The other one is this: There has been described only a hypo-sensitivity reaction to ozone. Almost by definition, an induced hypersensitivity reaction in the sine qua non of an allergic response. Is there any evidence that response to a subsequent exposure is intensified, compared to the response to the earlier or sensitizing exposure?

In other words, hyposensitivity may be a somewhat debatable phenomenon and the exact mechanisms involved, to say the least, are obscure. However, one should expect hypersensitivity here, if this in fact has an immune basis.

DR. SCHEEL: In answer to your last question: If you expose the rabbit daily, you don't obtain any circulating antibodies, and I think this relates to Captain Babione's discussion of how you harden an animal. In eleven months of exposure of eight rabbits we obtained only very sporadic positive results; until at the end of the exposure after we let the rabbit go for seven to ten days after the last exposure. All the time during the exposure antibodies were there, but they were not freely circulating because of the daily exposure. After stopping the exposure they became free to circulate and were found. In regard to manipulation of exposures, to see if you can challenge them and get a result which will lead to the idea of hypersensitivity; lets's go one step further back and see what kills the animal, with regard to ozone. This is what we are talking about in terms of tolerance. In terms of tolerance, we say that the exposure to ozone at sub-lethal doses will cut down the mortality rate of subsequent exposures. This we call tolerance. The ozone death, on the other hand, is due to the filling of the lung with edema, which is not necessarily the result of chemical irritations. We have the edema reaction, which reaches its peak somewhere between four and twelve hours after the ozone exposure is finished. This edema reaction on primary charge can be made fatal if the concentration is high enough. On the other hand, if you pre-expose the animal, you protect him against the production of edema, and thus he does not die. This is what we are talking about.

I don't know exactly what part this mechanism plays in that reaction. This is a rather complicated subject.

In regard to your first question: Can you manipulate the concentration, so as to get a hypersensitivity reaction? I have not done any of these experiments because there were questions, such as: Can you passively transfer the ozone specificity with your antigen? Very, very preliminary results on that indicate that not only can you passively transfer this sensitivity, but it may have an effect on the edema reaction.

I want very much to do a great deal more study on this part of the work, and to investigate the pathological developments after ozone exposure on specifically immunized animals. I think we may find things which determine the pathology of the ozone reaction and what will develop on repeated exposures. We may find out some answers to the questions you asked, Dr. Nelson.

DR. HEIMANN: We will now proceed to Panel VII.

## PANEL VII

## COMMUNITY HEALTH STUDIES

DR. MANCUSO: The first presentation is the "Detroit Pilot Study Of Community Air Pollution And Health," and will be given by Dr. Fredrick of the Detroit Department of Health.

DR. FREDRICK: This pilot study that I am reporting required three and a half years in the "make-ready" period, two and a half years for collecting the data, and, thus far, two years to analyze the data. So, in ten minutes of time I am reporting on eight years of work.

I want to make this preamble: Everything that I say here is my own opinion. I am not a spokesman for any group. I am simply offering my own interpretation.

The study originated in the Detroit Health Department, which wanted to find out if the levels of air pollution in the city were having a measurable effect on the health of the population. We succeeded in evolving a design of study which I won't go into at all, since I think, it is outlined briefly in the abstract. We are still quite satisfied with the design, as far as trying to get an answer to this sort of a question is concerned. From the standpoint of learning how to execute a large community epidemiological study of this type, we have had great success; we learned a great deal, and the pilot study was well worth the effort we expended upon it.

This was a study to determine the acute health effects. It was not designed to provide data on chronic disease in the population.

What happened was this: We had three study groups. With one pair of groups it turned out that the pollution was about twice as high in one section (group) as it was in the other. We found a little more sickness in the group that was exposed to the higher level of pollutant. In terms of air pollution there was a 2 to 1 ratio.

1. On the amounts of sickness the ratio was about 1.26.

The next pair of two groups that we had, it turned out was exposed to similar levels of pollution. We had intended that they would be exposed to different levels; but, it came out that they were exposed to about the same level, and they showed the same amount of sickness. The third was a Negro group, and we wondered if there was going to be a different type of reaction with this group.

2. We find that the Negro group may not be suited for this type of study. We turned out with slightly more illness in the low-pollution area than we did in the high pollution area. The major reason why the results of this study, as far as its effect on health is concerned, are indeterminate is because of a clash of ideologies. In my opinion there are two ways that one may look at this type of study:

From the standpoint of execution of the study design, we have the pragmatical approach, in which one goes out to do the best he can with what he has, and doesn't worry about the myriad of details.

And, then, we have the purists, on the other hand, who wish to tie every one of the factors down as close as possible, in order for the results to have any meaning when subjected to analysis afterwards.

There is no way, it seems to me, of resolving the argument between these two schools of thought at this stage of our knowledge. This is so because nobody has ever run through studies of this type. That can only be resolved by doing the job over again. If by doing it over again and paying a maximum of attention to fine details we obtain no significant change in the results, then one can conclude that the earlier pragmatic approach was satisfactory.

Here is what we learned from the pilot study, and we feel this was well worth the effort we expended on it:

1. Air pollution in the Detroit-Windsor area that we had under study behaved as a system. It is not a random, disconnected thing. It behaves as a well-organized system.

2. A 12-month period of observation is necessary (and sufficient) to complete a cycle of observation, as far as the environment is concerned. You cannot do it in less than 12 months but, a 12-month period is adequate and not much is gained by extending it for a longer period of time.

3. We also found that seven-day-a-week observations are necessary. They must be continuous. You cannot integrate a sample over the weekend, for example, because the integration process leaves you with gaps of some vitally necessary information when you try to interpret the data.

4. If we were to do it again we would add certain ambient carbon monoxide measurements. We would increase the sensitivity of the sulphur dioxide measurement; and we would include measurements of natural radioactivity.

5. We also demonstrated that in a suitably selected, fairly finite population area that you select for study you need

only one sampling station to define the air pollution stress in that area. (In Detroit).

6. As far as the sickness study is concerned, a one-year period of observation is adequate. On the other hand, a period of observation of less than one year is insufficient because of the fact that sickness follows in a pattern which is cyclic through a year. We ran two and a half years. The second year repeated the first and in the next half year we were repeating the first half-year cycle.

7. We also have found that one needs to use only one low test area and one high test area, because there is no indication at all that running more areas is going to yield any more information or substantially increase the reliability of the data.

8. We also found out about how many families you need to put into a study area in order to make it work. We have had groups of different-sized numbers of families as we went through some of these study areas. But we have found now that for a study of a duration of one year, 100 families in each area is adequate; 100 in the low pollution area, 100 in the high pollution area. In Detroit that runs a little more than three to the family, which will give you the sort of numbers we are dealing with.

9. In the matter of getting the information about the daily run of sickness in this family group, as would be given to you by a spokesman or reporter for the family group, that information is going to have to be collected daily from the individual. It might be possible to let it skip for two days, but you certainly cannot go any longer than that. In this particular study we waited two weeks, and, using a calendar-diary technique, we found that the two-week period is too long. Trying to work back on the report of sickness on this calendar, in respect to how many days it had been since the last visit of the interviewer, we could see that you would not want to go much more than two at the most, and you would be much better off if you got it daily.

10. We now know that it is necessary to keep all of the data current, keeping up a reasonable degree of data processing as you go along. In other words, you must process your data currently, if you are to be able to watch the situation.

11. Machine methods for analysis of data are of dubious value, except for confirmation or testing of results obtained by hand tabulation, calculation, plotting and study. After you have gone through and sampled the data here in many different ways, and done the work by hand, and seen the trend and the possible relationships, then you can design a method of feeding this information to the computer that you are going to use only then you can ask the computer to verify what you have already calculated by hand, or suspect by examination of the data.

12. We used the Cornell Medical Index as a tool to try to study sickness frequencies. It appears to be a useful tool. The index coincided with our sickness survey data. This may well be fortuitous.

13. One gets the impression that if the increased acute sickness found in the higher pollution area is significant and real, it is probably due to a higher incidence of chronic illness in the study population, rather than a direct response to rising and falling of the ambient pollution level. Although more work can be done with profit on acute health effect studies, ways and means must be found for detecting possible increase in chronic illness of populations living in polluted urban atmospheres.

I mentioned that we found that the Negro families were not satisfactory for use in such studies. We found that the Negroes do not report the ordinary run of acute sickness that the white population does. It was a great surprise to us to see the very low incidence of complaints in the Negro group. We investigated this and found that the rate of absenteeism of Negroes in certain worker groups is below that of the white. Of course, the low sickness response might have been due to ineffectiveness of the interviewers used in the Negro population groups rather than a real difference.

We concluded that we just do not know enough about the Negro population, or their whole general response, to use them in a study like this.

DR. WENTWORTH: I am somewhat familiar with the Detroit data. With Dr. Fay Hemphill, I had the privilege of reviewing some of the data which Dr. Fredrick was discussing this morning. We both felt that a considerable amount of data on the air pollution side of the study had been collected which might be very valuable. I was sorry that Dr. Fredrick did not bring out some of the analyses that he has done, especially in comparisons of the level of pollution in relation to changes in wind velocity and direction and so on. I think there might be some very excellent leads in that data.

On the health side, we were forced to conclude that due to lack of direction in the collection of the data, and principally, I think, due to a lack of current editing of the data and proper training of the interviewers, it was extremely difficult, if not impossible, to place very much validity on the morbidity data. It was our feeling that a conclusion, either as to association with air pollution, or the lack of it, probably should be held in abeyance.

We thought that the original design, the concept of comparing daily occurrence of illness in a high pollution and low pollution area within a city was sound and that the basic design of study was reasonably competent. The sample was probably adequate. The fault lay in the methods of collection and current analysis of the medical data.

I would agree with Dr. Fredrick that because of certain problems in Detroit, especially the fact that there is an international problem, this might be a suitable place to repeat the study, provided that certain details were taken into account that had not been before.

DR. KORNS: I am not familiar with the details that were not presented here. I gather that the comparison between these high and low pollution areas was in terms of total morbidity as gained by these bi-weekly interviews in the household. I wondered to what extent the morbidity can be categorized into types of morbidity; was this done; did the sample size not allow breakdown in this fashion?

There is another point bearing on the same consideration: Was there an attempt to correlate the daily score of illness as recounted two weeks later with the actual pollution at the time in that particular area, or was it a gross comparison of a low and a high area? If it was the latter then you face up immediately to other elements or characteristics of the samples in these two areas that have bearing on illness, the socio-economic levels, and the extent of medical care.

When you mentioned the sample size that you might shoot for next time, 100 families in each area, the matching of these adequately in terms of all the pertinent characteristics would be quite a feat. I wondered whether you could dwell on this area a little bit longer.

DR. FREDRICK: We made every effort to match the population groups from the socio-economic point of view. A lot of time and money was spent on that. We think that the census tract areas that we were using were about as similar in population characteristics as we could get them. The data would indicate we had done a pretty good job of matching.

Now, you were asking about how far did we break down the symptoms. We broke them down as far as they could be broken down, and, of course, the question comes: How much work do you want to put on it? Some symptoms occur too infrequently to be of much consequence. Other symptoms are numerous enough that you can work on them. So long as there is a question as to whether the data is reliable, anyway, because of the methods of its collection, and the execution of the design, I do not think it is worthwhile to go too far. We decided to stop. The data is all ready on IBM cards at the present time, and detailed studies could be made.

DR. CIOCCO: I think that Dr. Fredrick has really said something which we are going to hear time and time again in regard to community studies. This is, that to make a good study, one that will give definitive results, a good deal of time must be spent in planning and in organizing it, and we should be prepared to spend money. I think that this is the lesson we learn from Dr. Fredrick's work. It took them eight years to realize it. Perhaps, it has been a little too long. Nevertheless all of us have to go through a similar stage.

Another point which Dr. Fredrick made is that you cannot expect the IBM equipment to ask your questions for you. You have got to ask the questions first -- and intelligently -- and then, perhaps, the IBM will help you.

I was surprised at his statement regarding the Negro, and their sickness pattern, which is at variance with our experiences in Baltimore, in Pittsburgh, and in other places. It must be a reflection of something unique about the Detroit area.

I would have liked to ask the same question that Dr. Korns asked, regarding how you are going to go about selecting your samples now, and how are you going to plan on finding out about illness or sickness? In your answer to Dr. Korns' question, you seemed to indicate that you are going to define illness afterwards. I wonder if this is wise, inasmuch as you are going to have to ask some questions, and you are going to do something with the data. I wonder whether or not you should not be doing some thinking now as to what you are going to do with the data on illness or the data on something which you are going to define as illness.

DR. ZEIDBERG: I am wondering whether the Negro, as a respondent, in comparison to the white person as a respondent, may not involve a practical problem.

DR. SHEPHARD: I think there are many comments that should be made on this presentation. I am just going to content myself by referring to two of them.

One of the factors which has been of particular interest to us here in Cincinnati is this question of whether one can characterize a medium-sized city into areas of high and low pollution. We have been operating some 60 or 70 continuous smoke sampling devices in the homes of our patients throughout the city and we found that at different times of the year different levels of pollution exist in different parts of the town. As shown on the slide the level of pollution during the winter is much higher downtown than it is in the more outlying areas; but, during April the load of pollution in the downtown area is almost identical with that in the outlying area. It depends a great deal on the wind direction during the particular month in which you are interested. The level of pollution may be quite high when the wind is blowing from an area where you have an industrial plant. If it is blowing in the opposite direction, it may be quite low.

It also depends on whether you have the windows open or closed in your house. The level of pollution in a house where the windows are closed is only about 40 percent of that experienced in the house where the windows are habitually kept open. I think that illustrates some of the fallacies which may arise from trying to characterize areas of a town, as having "high" or "low" pollution.

The other point refers to this question of multiple regression analysis. I agree that it is necessary to have some hypothesis before you put data into one of these electronic computers. But I would dispute the contention that it is always possible to visualize figures on a graph before you put them into a computer. We have found that there are about six or seven factors which were affecting the health of patients. You have linear and quadratic trends in their general condition which are completely unrelated to air pollution. You have the effects of water vapor and temperature, effects of smoke, and effects of sulfur dioxide independent of smoke. The result is that you have seven different factors affecting the health of your patients, and each may have one of ten possible different lag periods. If anyone can tell me how you are going to draw a seven dimensional graph with ten different lag periods, and see what is going on, I would be interested to hear about that.

I think it is very important though, that we do not just throw this data haphazardly into the electronic computer. I think it is very important that the person who is operating that computer should know a good deal about human physiology and the nature of the reactions to air pollution.

DR. CHAMBERS: I would like to add one word in that connection. We had a modest amount of experience in monitoring atmospheric parameters potentially involved in this type of study, and I must admit I am a little bit confused by the rather categorical generalizations that I heard this morning in this last presentation with respect to the adequacy of the sampling procedures, the mathematical procedures, and so on. The confusion arises from the fact that at the outset I understood that there was general agreement that the results of the study, with respect to the objective, have been indeterminate. It would seem to me that with an indeterminate result there can be no establishment of the fact that a particular procedure has been effective.

DR. WRIGHT: I would like to ask a question somewhat along the same line, with regard to interviews. Was any effort made to learn the repeatability of an interviewer with a single individual and the repeatability of two interviewers interviewing a single individual?

DR. FREDRICK: I should like to make a few closing remarks. One is that I doubt if there are many areas in the United States that are as suitable as Detroit for studies of this type. We had to do a tremendous amount of exploration to pick our areas in Detroit. Detroit happens to be a city of flat terrain and it has an unusual distribution of its sources of pollution, in respect to residential areas; so that we could pick residential areas that were getting a diffuse type of pollution. There was no single source that was predominant in a study area. Also our socio-economic structure did not follow any particular pattern. As a matter of fact we could have picked a very high income group that was in a very high pollution area but we did not consider they were suitable for study. We were not interested in that group.

As far as the major question is concerned, we still think the design of the study is all right. Our fault lay in the execution of the design, and, in many instances, we knew we were cutting corners, or we were having difficulties of execution because we did not have the proper kind of financing or staff personnel. In other cases, we did not know whether it was necessary or not to do a certain thing. We have learned a lot by going through this pilot study, and we have learned a lot about dealing with the interview technique. We think that we know how to shore up that interview technique, using new methodologies that have been developed since this study was conducted. I think we can meet that particular problem pretty well.

DR. MANCUSO: The next presentation will be on "Air Pollution Mapping In The Los Angeles Basin," by Mr. Landau:

MR. LANDAU: Medical research is increasingly concerned with the environment in which people live. Environmental factors have been found to have a profound effect on discomfort and illness. Considerable interest was attached, therefore, to the complaints of episodes of air pollution by the residents of the Los Angeles Basin. This is an area of some 1600 square miles in which about five and a half million people are living today.

For the past ten years, the "oxidizing" type of air pollution present in Los Angeles has led to complaints of eye, nose and throat irritations. Also, the haze and the attendant reduction of visibility, often marked, have prompted complaints on the part of the inhabitants. Most observers in the Los Angeles Basin have realized that air pollution has not been uniformly distributed throughout the Basin. For our purpose, we took the Basin to consist of the portion of the Los Angeles Coastal Plain in Los Angeles County, the San Fernando Valley region, and the San Gabriel Valley region.

It has long been recognized that the intensity of air pollution tended to increase, within certain limits, with the distance from the coastline. Obviously, therefore, the practice of using the level of air pollution as recorded by the monitoring station at downtown Los Angeles or at Pasadena, for example, as a gauge of the entire area, was subject to considerable limitations. Accordingly, we felt it would be valuable to analyze the air pollution pattern and differentiate the area in terms of air pollution levels. This map would be of value in studying the medical effects of air pollution. Some progress in preparing such a map had already been made. A freehand map had been prepared by the Los Angeles Air Pollution Control District in February 1957, which delineated four areas with varying degrees of air pollution. It was based on the following data: (1) knowledge of local topography and meteorology; (2) analysis of air pollution measurements; and (3) spontaneous complaints of eye irritation by inhabitants of certain areas. After examining that map, we felt it desirable to prepare our own version, using systematic data regarding biological reactions to air pollution as well as chemical measures.

Accordingly, we made use of three measures; namely, chemical, botanical and social. The chemical measures used were: (1) the monthly mean maximum "oxidant" value for 9 APCD measuring stations; (2) the number of days during calendar 1956 that total maximum oxidant reached 25 parts per hundred million or higher. For the botanical measure we used daily data on plant damage for 11 APCD stations for both 1955 and 1956, and data for 5 additional stations for either 1955 or 1956. Our social or biological measure was the proportion of persons "bothered" by air pollution as reported in the California Health Survey of 1956.

The measures used incorporated the types of data that were available. Thus, for the chemical measures, we were restricted to using oxidant levels because the other measurements -- carbon monoxide, aldehydes and particulates -- were either incomplete or showed very little variation. An analysis of the oxidant data for 1954 indicated that these data would contribute little to the study and, therefore, they were not used. The selection as a criterion of the number of days that total maximum oxidant levels reached 25 parts per hundred million, was based on the knowledge that this is a level at which many people begin to experience eye irritation. The measure of "being bothered" by air pollution was used in preference to spontaneous eye irritation complaints because of the more systematic basis of the survey data in which the former was collected.

On preparing the map, our first approximation consisted of comparing each of the 9 stations with every other station for significant differences in the mean maximum oxidant values. Where the data were not completely consistent for the entire year, primary emphasis was placed on the Fall values, i.e., September to December. For the subjective measure, represented by the proportion of persons "bothered" by air pollution, we had data from 88 communities or area designations, with the number of respondents ranging from 1 to 152. To increase the stability of the figures, we omitted the areas having fewer than 10 respondents. We also omitted areas of indefinite designation. We found by these criteria that we had useful information for 36 communities. These areas were well differentiated with respect to the alleged effects of air pollution. The range of population "bothered" was from 13 to 94 percent. Ten of the areas showed that 70 percent or more of the inhabitants were "bothered" by air pollution.

The techniques for preparing the map consisted of setting up a set of "overlays" for each of these measures, followed with a final "overlay" which incorporated the common features of most of the measures. Areas having relatively common characteristics for any given measures were linked. As we expected, there was not complete agreement among all the measures and patches of relatively "intense air pollution" for a given measure could be found in a band of "moderate air pollution" for another measure. Furthermore, the stations used for chemical measures were usually some distance from the stations obtaining plant damage data. Accordingly, the map represents only an approximation of the situation that exists in 1955-56. It is of interest that the map, in general, is in relatively good agreement with the Los Angeles Air Pollution Control District map, already mentioned. We found in comparing the maps, that there was good similarity, and that in general the area which was furthest from the coastline tended to be the area which was least heavily polluted.

Basically, the map prepared by us shows that our area of high air pollution density corresponds roughly with Los Angeles APCD Areas 1 and 2. Their Area 3 corresponds roughly to our Area 2. Their Area 4 corresponds roughly to our Area 3. The correspondence between the maps was quite good.

Because of the necessarily inexact nature of the map, the decision was made to delineate the intensity of air pollution in terms of statistical areas, rather than communities or individual census tracts. The use of individual tracts as boundaries would have necessitated a substantially larger number of judgments and might have implied a degree of accuracy which was not warranted by the data used. Further, much of the information available in the basin at this time is for large statistical areas rather than for census tracts. Also, since the statistical areas are combinations of census tracts, and do not cut across tract boundaries, population and other data collected by census tract can still be used in analytical work.

Mapping the area should prove of value for at least three types of studies: First, it may make it possible to study the acute effects of air pollution on mortality in the basin in a more systematic fashion. Within a relatively narrow band of temperature ranges, it may be possible to establish two or three areas of differing air pollution levels. Since the areas do not cut across census tract lines it becomes possible to take into account, and possibly to control, the demographic characteristics of the areas. Second, mapping should be helpful in studies of morbidity in the area and may furnish leads to the long-term effects of air pollution. Thus, a survey which attempts to measure the prevalence of chronic respiratory conditions, for example, can be made more meaningful if it is possible to take into account the relative degree of pollution of the area in which the respondent lives. Finally, such mapping may be of value in the study of automobile accidents as they may be affected by the level of air pollution. There may be a loss of judgment, in addition to the reduction in visibility and eye irritation, associated with severe air pollution. Industrial accidents, too, may be related in some fashion to the level of air pollution. Here, too, this relationship may be studied in a more meaningful fashion with the aid of the map.

We feel that revisions of the map may be necessary, as more complete data are made available. Nonetheless, the fact that a provisional map can be prepared for Los Angeles indicates the possibilities of such an approach for other areas.

DR. KORNS: You are combining several indices of air pollution into one, with the hope, thereby, of ironing out chance fluctuations and making certain of including the really significant indices. Conceivably, you may inadvertently be camouflaging some important single element. This is something that I am sure you would try to guard against.

I am a little disturbed at your use of the item "public reaction to air pollution," as one of your indices. If, later, you are going to use the map as a basis for comparing morbidity in different areas you conceivable might already have introduced an element of bias in selecting the areas, since you have used this attribute related to health to set up the area standards initially. Do you think that this is anything to be concerned about?

MR. LANDAU: I think the answer to that would be that this map was composed of several types of measures. In general, the fact that you do have eye irritation in a given area corresponds roughly to the fact that you have levels of oxidant and other chemicals in the air which apparently do cause eye irritation. There are people who apparently do not suffer eye irritation, no matter what the level. There are others who have eye irritation at very low levels of oxidants. But eye irritation is associated with oxidants in air. The fact that people react to a given level of oxidant, I think, would probably not change their pattern if they moved from one area to another.

This is actually a medical or biological response to a given atmospheric contamination level. And I am not sure that this fact that they respond would have any effect on whether or not they tend to be more or less subject to chronic bronchitis, for example.

DR. HARRIS: It seems to me that you have a possibility here for an application of a method that I should like to discuss.

For one thing, if you want to discuss a particular element, like oxidants or nitrogen-oxides, it is true that you can make up a special map. Maybe that is a good thing to have. It can have uses. But, if you want to give each element equal weight then, instead of dealing with each element separately, I think it is worthwhile to realize that the elements are highly correlated among themselves. Instead of using ten or fifteen elements separately, from which you may derive perhaps two or three functions which may account for a large proportion of the over-all variation in the ten or fifteen elements, you can arrange your map on the basis of values of those linear functions, which will essentially give you about as good discrimination as you could get by trying to overlap these measurements individually. You already know that, in fact, they are highly correlated with each other. So I would say that here is an application for the method of principal components, a branch of factor analysis theory.

MR. MANOS: I would like to say that I believe Dr. Korns' comment is well-taken. However, that would not be a problem if you use the areas to study the acute response through time, because you have merely separated out the area where this response would be most expected. You have reason to expect that the response would appear more frequently in one area than in the other.

DR. CAREY: It was of particular interest that Dr. Landau mentioned the question of industrial accidents during periods of smog. We looked through the records of two large industrial concerns in Cincinnati and found that in their 21,000 employees there did not seem to be any significant difference in accident frequency in relation to air pollution.

DR. MANCUSO: Our next presentation will be the "Acute Effects Of Los Angeles Air Pollution On Patients With Bronchial Asthma," by Dr. Schoettlin:

DR. SCHOETTLIN: In order to observe the effects of community air pollution on persons with bronchial asthma, a study was done during the fall months of 1956, using known asthmatics who lived in Pasadena and neighboring towns. In this area: (1) bouts of air pollution were often severe; (2) air pollution monitoring devices were in operation; and (3) several local physicians were concerned about the effects of air pollution on their own patients.

Five physicians cooperated in the project by selecting from their patients a total of 157 patients whom they were treating for allergic bronchial asthma. The selected patients lived and worked in the foothill region of the San Gabriel Valley, an area measuring 5 by 15 miles. Twenty of the 157 patients chose not to participate in the study. Analysis of reasons given for non-participation revealed no evidence of systematic bias created by loss of that group.

A compilation of the incidence of asthmatic attacks was made on a current basis for the study group. Each physician sent a form letter to his own group of patients asking for a mail report of every attack of asthma which each patient had from September 3rd through December 9th, 1956, a period of relatively severe air pollution in previous years. The patients mailed their reports to the physician each week. If no report was received during a given week, the missing record was solicited by telephone by a member of the study staff. At no time were the terms "air pollution" or "smog" mentioned to the patient. The private doctor-patient relation was maintained throughout the study.

Data supplied by the patients were then coded for machine tabulation. We studied each attack for: (1) time of onset; (2) severity of the attack; (3) where the patient was when the attack occurred; and (4) the patient's opinion as to the cause of the attack.

Air pollution and weather data were supplied by the Los Angeles County Air Pollution Control District from their downtown Pasadena monitoring station. Meteorologic data included temperature and relative humidity. We selected hourly averages of continuous recordings of total oxidant, total particulates, and carbon monoxide as indexes (measures) of air pollution for this study. Daily pollen counts and air pollution plant damage observations were also made in Pasadena.

Equal numbers of males and females were included in the study. The age distribution of the asthma study group corresponded roughly to that of persons who said they had asthma when interviewed for the California Health Surveys of 1954 and of 1956.

You will note from the first slide that the peak duration of the asthmatic process in the 137 patients was ten years or more. Most of the patients lived in the basin for ten years or more. We found that those patients who had lived in the basin less than five years had their asthma before they came there, while those who had lived there five years or more developed the disease after coming to the basin. Apparently, we were working with a fairly stable population.

The next slide indicates the timing of attacks reported by the patients. The daily number of attacks was 35.1. You will note that the period of midnight to 6 a.m., was the peak period for attacks of asthma. In contrast, the 11 a.m. to 4 p.m. period was the one showing a peak for air pollution, as measured by total oxidants.

The next slide shows that asthmatic attacks occurred roughly in proportion to the number of persons for each age group. You will note that the younger patients possibly had slightly less than their proportionate share of attacks, while the older patients had a somewhat greater number. Males and females had equal numbers of attacks. Ninety-five percent of the attacks were described by the patient as being "mild."

The patients were asked to report what they considered to be the cause of each attack. We were surprised to find that in almost three-fourths of the cases the patients could not describe a suspected cause. Air pollution, temperature changes and weather changes, each accounted for five percent of the attacks, according to the patient's estimate. Respiratory infections were blamed by them for 10 percent of the attacks.

The relationship of frequency of attacks of asthma to the various gauges of air pollution was studied. The correlation between the total number of daily asthmatic attacks with simultaneous measures of total oxidants was found to be greater than with any other chemical indices of air pollution studied. Only one-seventh of the variability in the daily attack rate was associated with the variability of total oxidants. The specific figure used was the maximum hourly average of total oxidant during each 24-hour period.

The next slide shows a scatter graph diagram in which each of the asthmatic attacks was plotted against total oxidants. No consistent pattern was shown here. Temperature, relative humidity and water vapor pressure also showed a low positive correlation with frequency of asthmatic attacks. The correlations were numerically smaller than the correlation between oxidants and attacks. In analyzing the association of total oxidant with asthmatic attacks, we must remember that total oxidant is correlated with temperature, as shown in the next slide.

The study also tested the extent of agreement between medical and botanical reactions to air pollution. This we did by examining the distribution of attacks of asthma against days with and those without air pollution plant damage. The difference in the mean number of attacks for all patients on days with and on days without plant damage was significant at the five percent level, but not at the one percent level. We noted that patients who had lived in the Los Angeles basin ten years or longer had a significantly larger number of attacks on days on which plant damage occurred, while persons residing there a shorter time did not. Additional analysis revealed non-homogeneity of the population, when broken down by residence in the Los Angeles basin, and severity of asthmatic process.

Some of the patients had no attacks during the study; some had attacks mostly on days of little pollution; a third group often had attacks on days with pollution. It was felt that even though all asthmatics do not respond to air pollution, perhaps this third group could provide some clue as to the reasons. The search for a common characteristic was fruitless in this group of eight persons. There were seven females and one male among these "smog reactors;" they differed in their age distribution and severity of the disease.

In summary: (1) Asthmatic attacks in the group under study occurred equally in males and females; (2) the time of day in which there were the most asthmatic attacks was midnight to 6 a.m.; (3) there was a low positive correlation between attacks of asthma and maximum total oxidant levels, indicating that about one-seventh of the variability in the daily attack rate was associated with variability of oxidants; (4) eight selected asthmatics, whose attacks corresponded to days with air pollution, showed no common characteristics, in regard to age, severity of illness, duration of illness, duration of residence in the Los Angeles basin, or known sensitivity to allergens. Seven of the eight were females.

DR. CIOCCO: I would like to comment on some of the statistical aspects of the report and raise some questions. As Dr. Schoettlin has noted, his group is heterogeneous in certain of its characteristics. The question I would like to ask in that regard is whether or not the group is homogeneous with respect to the disease itself, *i.e.*, asthma. Are there ways in which the group could, from the standpoint of clinical knowledge, be logically divided into homogeneous groups with respect to disease? Dr. Schoettlin finds a low-order positive correlation, or, to all intents and purposes, very little correlation of any kind. This is why one suspects that perhaps he is dealing with a heterogeneous group. The other question is in regard to the observation on the variation among individuals in terms of the number of attacks. Apparently, the average number of attacks was not spread uniformly among the individuals. There was some who had none and some who had a lot. I think that a little more analysis of the data from the standpoint of individual distributions of attacks might be useful.

A third point which I would like to bring out is that perhaps there are other ways of analyzing the data other ways in which to ask a more direct question regarding the relationship between asthmatic attack and changes in the pollution level.

DR. STOKINGER: From our toxicologic work we may have some connection in regard to these oxidants. We presented this information last year, but we may not have emphasized it, or it may have gone unnoticed. We did some work on the toxicity of organic peroxides and hydrogen peroxides and noted that while they were not in any case highly toxic, in small doses they exerted a cumulative effect. Thus, in a period of seven weeks, with doses that should not have accrued to significant effect, we observed deaths when the material was given by several routes of administration. These organic peroxides give cross-tolerances with ozone and with hydrogen peroxide.

CAPTAIN BABIONE: I wonder if Dr. Schoettlin may not be on the wrong track. In this part of California I have noticed that night distress in respiration is a very common thing. It begins a few hours after dark and gets progressively worse during the night. It seemed to be related to cold -- damp night air -- rather than to any allergen. This was so common in my experience that I made a great reputation telling these people to sleep with their bedroom windows closed. When they did that, they were quite free of the trouble.

DR. CAREY: I would be interested to know what the diagnostic criteria were for the diagnosis of asthma.

DR. ZEIDBERG: I wonder whether any effort was made to obtain pollen counts and perhaps to correlate thse with the attacks?

DR. SCHOETTLIN: In answer to Dr. Ciocco's question. These patients were all diagnosed by internists as having bronchial asthma. We definitely felt we had two different diseases, one in the young children up to about age 15 and the other in older people in their fifties and over. My explanation, is that the youngsters had a true allergic phenomena. In the older people the disease was probably an infectious process.

Our criterion of asthmatic attack and its severity was the four-level system used by the Association of Clinical Allergists. On their scale "zero" level is when there is an attack of wheezing that clears spontaneously, without medication. The second level they use is wheezing which clears with medication. We included these as mild attacks. A moderate attack of asthma corresponds to their third classification, which is when there is an attack of wheezing which is associated with a loss of time from work, or that the patient feels he is no longer able to carry on his usual duties. The fourth level that they have, which was our severe asthmatic attack was one which requires at least intravenous medication, and often hospitalization.

A pollen count was taken each day throughout the study. There was a very slight positive correlation with level of pollen count, on a daily basis.

DR. SUSSMAN. Did you divide the cards into therapeutically responsive groups? On the postcards that patients sent in, did you have any question about those receiving medication during asthmatic attacks, medication that would influence the severity of the attack?

DR. SCHOETTLIN: No breakdown on the basis of therapeutic groups was made. We classified our patients by severity of disease. This was based on a two-year retrospective look at the patient's visits to the doctor and his hospitalization record. We asked the patient to grade his attack.

Then he was asked what medication he had received, to see how severe the attack was.

DR. CHAMBERS: I have one comment, prompted by Captain Babione's remark. It seems to me that in addition to a lack of homogeneity in the population under study, there is also a lack of homogeneity, perhaps, in all of the environmental measures that were used. I believe that an index based on oxidant is a rather meaningless concept in specific terms. An "oxidant" as used here, is anything that will cause a color reaction under appropriate conditions. That can include a lot of things, some of which may be irritating in respect to the lungs, and some not.

The observed distribution of asthmatic attacks in the night, along the coast, suggests to me the possibility that sulfur dioxide might be involved. In spite of the map that was shown here, a distribution map similarly constructed for concentrations of sulfur dioxide will indeed show that sulfur dioxide and trioxide are at their maximum along the coastal areas at night. In other words, in addition to being a little more specific about the population groupings, those of us measuring the environment need to be a lot more specific about what we are measuring.

DR. MANCUSO: We will now go on to the next presentation, "Effects Of Naturally-Occurring Air Pollution On Chronic Bronchitis -- Methodology," by Drs. Breslow and Goldsmith and Mr. Buell. Dr. Goldsmith will make the presentation.

DR. GOLDSMITH: In the studies from the California Department of Public Health we have examined mortality data and morbidity data without finding any acute effects which could be associated with air pollution. We are becoming more concerned now with long-term effects, with altered function and with aggravation of existing illness, that may be associated with breathing dirty air. This report is concerned with the last category.

In 1956 the Department conducted a State-wide household sample survey to determine, among other things, the effects of air pollution on health and well-being. The sample consisted of 3,545 households. From each of these, a randomly predetermined adult was asked concerning sixty items about his health in general and concerning the presence of various chronic conditions and the factors which he thought made them worse.

Up to that time "air pollution" was not mentioned to the interviewee. Finally, in the survey, a question concerning whether or not the respondent was bothered by air pollution was asked. But, the spontaneous mentioning of air pollution as an aggravating factor by these respondents was sufficiently frequent to focus our attention on the possibility that chronic respiratory disease was aggravated.

In this group of people, excluding all those under thirty years of age, 108 reported that they had bronchitis, 47 reported that they had asthma, 28 reported both bronchitis and asthma, 263 reported cough with some disorder such as hay fever or sinusitis, and 69 reported coughing alone without an acute illness to which it could be ascribed.

## TABLE I

(See Page 182-A for Table I.)

Our study is a follow-up of these 515 individuals, conducted by interviews planned for three times per year. It is intended to determine the incidence of morbidity, including medical attention and hospitalization. We have, so far, conducted two interviews. In this panel of persons with chronic respiratory illness it was found that for both the panel and the survey about two in five were from Los Angeles. In other words, the distribution was approximately what would have been expected. Of those reporting chronic conditions, the relative number with bronchitis, asthma and cough was about the same for Los Angeles, the San Francisco Bay Area, and the remainder of the State. But eye, nose and throat complaints were more prevalent in the Los Angeles respondents while sinus trouble and hay fever were less prevalent.

The hypothesis on which our study is based is that, other things being equal, persons with these disorders who live in an area of high pollution have greater morbidity than persons with the same disorders who live in other areas. The data for testing this hypothesis has, I regret to say, not yet been compiled. Nor is it certain that the population is large enough, or that the method is sufficiently specific so that an unequivocal answer would be a reasonable expectation. On the basis of two interviews which we have had, one starting in July of 1957 and the second in November of 1957, we should like to present some observations relevant to the method and to list some of the assumptions and qualifications underlying our proposed analysis.

The first follow-up interview occurred in July and August of 1957. The respondents were asked about level of health, about bronchitis and asthma by name, and about the presence and nature of cough, sputum, and dyspnea and also about the morbidity related to these conditions. In addition, a detailed occupation, residence and smoking history was obtained. Where indicated, permission to obtain information from the patient's physician was secured. The questionnaires to physicians were mailed in September 1957 and of 183 sent, 162 were returned.

The second interview does not contain occupation and smoking questions. There was also some slight modification of the elicitation of history of cough and dyspnea in an attempt to increase the number of positive responses.

Table I summarizes the results in the first interview. I would like to call your attention to a few items in that table. In the first place, the boxed entries represent the number of individuals who remained in the same category of either symptom or diagnosis between the 1956 interview, which occurred approximately

# TABLE I

Percentage Distribution of Chronic Respiratory Conditions Reported in the California Health Survey, 1956, Tabulated by Conditions Reported in First Interview, (Jul-Aug) 1957

| Conditions Reported in California Health Survey, 1956 | Conditions Reported in First Interview(Jul-Aug) 1957 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Asthma | Asthma c̄ Bronchitis | Bronchitis | Cough c̄ | Cough s̄ | No Symptoms | Not Seen | Moved | Deceased | Refused | Senile[3] | Percent Total |
| Asthma | 40.4 [a] | 12.8 | 6.4 | 2.1 | 6.4 | 12.8 | 8.5 | 6.4 | 0 | 2.1 | 2.1 | 99.9 |
| (N=47) | (19) | (6) | (3) | (1) | (3) | (6) | (4) | (3) | (0) | (1) | (1) | |
| Asthma c̄ Bronchitis | 17.9 | 39.3 | 17.9 | 0 | 7.1 | 3.6 | 3.6 | 10.7 | 0 | 0 | 0 | 99.9 |
| (N=28) | (5) | (11) | (5) | (0) | (2) | (1) | (1) | (3) | (0) | (0) | (0) | |
| Bronchitis | .9 | 2.8 | 31.5 | 10.2 | 4.6 | 32.4 | 5.6 | 9.3 | .9 | 1.9 | 0 | 99.0 |
| (N=108) | (1) | (3) | (34) | (11) | (5) | (35) | (6) | (10) | (1) | (2) | (0) | |
| Coughing c̄ [1] | 1.9 | 0 | 6.5 | 28.9 | 20.9 | 31.6 | 2.7 | 2.3 | 1.9 | 1.9 | 1.5 | 99.9 |
| (N=263) | (5) | (0) | (17) | (76) | (55) | (83) | (7) | (6) | (5) | (5) | (4) | |
| Coughing s̄ [2] | 0 | 0 | 0 | 7.2 | 31.9 | 30.4 | 2.9 | 18.8 | 7.2 | 0 | 1.4 | 99.9 |
| (N=69) | (0) | (0) | (0) | (5) | (22) | (21) | (2) | (13) | (5) | (0) | (1) | |
| Total | 5.8 | 3.9 | 11.5 | 18.1 | 16.9 | 28.3 | 3.9 | 6.8 | 2.1 | 1.6 | 1.2 | 99.9 |
| (N=515) | (30) | (20) | (59) | (93) | (87) | (146) | (20) | (35) | (11) | (8) | (6) | |

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[1] Excludes asthma, asthma c̄ bronchitis, and bronchitis, but includes other respiratory conditions.
[2] Coughing only without any other condition.
[3] Senile includes incompetent, and too ill to respond.
[a] Percent remaining in same category is shown in box.
Note: Figures in parenthesis indicate numbers corresponding to percentages

at the same time of year, one year earlier, and the first 1957 interview. Approximately 30 to 40 percent of the individuals retained their same diagnostic or symptomatic classification. One of the things which surprised us was the large number, 14, who on the first interview in 1957 professed that they had no symptoms at all. This is shown in the sixth column in Table I.

Now, I also want to direct your attention to the source of these people. The entries in row 3 to 5 of this column show that thirty-two percent of the individuals who originally were said to have bronchitis, subsequently had no symptoms, and the proportion is about the same for the two categories of coughing.

## TABLE II

(See Page 184-A for Table II.)

In Table II you can see what happened between the two interviews in 1957. The response of the July-August interview is in the column to the extreme left, and in the column headings are the results reported in November-December interview, 1957. Here you will see that the stability within the diagnostic and symptomatic categories remains approximately at a higher level, in the 50 to 60 percent range. We made some special efforts to get the people who said they had no symptoms. We asked about cough in a manner suggested by Dr. Fletcher, and we used the question, as you can see from the schedule, as to whether or not they had any phlegm or sputum as an indirect way of finding out whether they had cough.

I would like to mention briefly our plans for evaluation and analysis before discussing some of our tentative conclusions. The first aim is a methodologic one, and it involves the determination of whether the size and character of our population sample were adequate to give a decisive answer. Among other factors, the following will be determined: (1) the loss rate due to refusals, moves, and so forth; we were gratified at the relatively low loss rate to date; (2) the incidence of episodes of ill health. If there are not enough people hospitalized, or enough who have sufficient illness to see a physician, it is going to be very difficult to make a comparison; (3) whether other risks, such as smoking or occupation, have so great an effect on symptom exacerbation as to over-ride a possible air pollution effect when the sample is a small one. The question of incidence is very important. The question of other risks may help to tell us what kind of samples should be observed. Now, if an effect is observed indicating greater morbidity associated with air pollution, one supporting test would be to see to what extent this morbidity is independent of the seasonal trend in respiratory disease prevalence which we have established in the 1954 California Health Survey.

Among the things I want to discuss is the large number of persons who first admit and later deny any disease or symptom. Let me just summarize the things that you find in the upper left hand part of Table II. The people who said "yes" both times were 233. The people who went from "yes" to "no symptoms", 31. From "no" to "no symptoms" -- that is, people who were found to have something in the 1956 survey, but did not have any positive response in either of the 1957 surveys -- were 74. And those who went from "no symptoms" to "some symptoms" or diagnostic groups, were 48. I think the difference between 31 and 48, if it is important, is some measure of the potency of the added method that we used in questioning about cough.

## TABLE II

Percentage Distribution of Chronic Respiratory Conditions Reported in the First Interview (Jul-Aug) 1957 Tabulated by Condition Reported in Second Interview (Nov-Dec) 1957

| Conditions Reported in First Interview (Jul-Aug) 1957 | Conditions Reported in Second Interview (Nov-Dec) 1957 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Asthma | Asthma c̄ Bronchitis | Bronchitis | Cough c̄ | Cough s̄ | No Symptoms | Not Seen | Moved | Deceased | Refused | Senile[3] | Percent Total |
| Asthma | 56.7[a] | 13.3 | 0 | 6.7 | 6.7 | 6.7 | 3.3 | 3.3 | 0 | 3.3 | 0 | 99.9 |
| (N=30) | (17) | (4) | (0) | (2) | (2) | (2) | (1) | (1) | (0) | (1) | (0) | |
| Asthma c̄ Bronchitis | 15.0 | 40.0 | 15.0 | 0 | 5.0 | 0 | 0 | 10.0 | 5.0 | 10.0 | 0 | 100.0 |
| (N=20) | (3) | (8) | (3) | (0) | (1) | (0) | (0) | (2) | (1) | (2) | (0) | |
| Bronchitis | 0 | 3.4 | 54.2 | 22.0 | 5.1 | 8.5 | 1.7 | 1.7 | 0 | 1.7 | 1.7 | 99.9 |
| (N=59) | (0) | (2) | (32) | (13) | (3) | (5) | (1) | (1) | (0) | (1) | (1) | |
| Cough c̄ [1] | 1.1 | 0 | 7.5 | 59.1 | 9.7 | 14.0 | 3.2 | 3.2 | 0 | 2.2 | 0 | 99.9 |
| (N=93) | (1) | (0) | (7) | (55) | (9) | (13) | (3) | (3) | (0) | (2) | (0) | |
| Cough s̄ [2] | 0 | 1.1 | 1.1 | 17.2 | 62.1 | 12.6 | 1.1 | 1.1 | 0 | 3.4 | 0 | 99.9 |
| (N=87) | (0) | (1) | (1) | (15) | (54) | (11) | (1) | (1) | (0) | (3) | (0) | |
| No Symptoms | .7 | 0 | 2.1 | 15.1 | 15.1 | 51.1 | 11.0 | 3.4 | 0 | .7 | 1.4 | 99.9 |
| (N=146) | (1) | (0) | (3) | (22) | (22) | (74) | (16) | (5) | (0) | (1) | (2) | |
| Not Seen | 10.0 | 0 | 10.0 | 25.0 | 5.0 | 15.0 | 0 | 20.0 | 5.0 | 10.0 | 0 | 100.0 |
| (N=20) | (2) | (0) | (2) | (5) | (1) | (3) | (0) | (4) | (1) | (2) | (0) | |
| Total | 5.3 | 3.3 | 10.5 | 24.8 | 20.2 | 23.7 | 5.3 | 3.3 | .4 | 2.6 | .7 | 100.2 |
| (N=455) | (24) | (15) | (48) | (112) | (92) | (108) | (24) | (15) | (2) | (12) | (3) | |

[1] Excludes asthma, asthma c̄ bronchitis, and bronchitis, but includes other respiratory conditions.
[2] Coughing only without any other condition
[3] Senile includes incompetent, and too ill to respond
[a] Percent remaining in same category is shown in box
Note: Figures in parenthesis indicate numbers corresponding to percentages

Relative to some of the questions that have been raised in regard to an earlier paper, we have compared the population who give a stable response and the population who give a differing response. One of the things observed with seeming significance was that the proportion of Negroes in the population who gave different responses was greater than in the population which gave stable responses.

Among the reasons considered to account for first reporting and then denying a condition or symptom are some of the following: First, reasons based on techniques: (a) the same set of symptoms or a disease may be described in different terms at different times by the same respondent; (b) we may have failed to exclude acute disorders in 1956, or in the earlier interview; (c) we may have failed to obtain adequate evidence of chronic disease in the later interview -- as was tested by our exaggeration of the question about cough.

Possibly there were clerical errors; or, possibly there were interviewer errors. These latter two reasons, I think, have been largely excluded by careful training and supervision on the project. Item (c) was explored by the provision of a somewhat greater number of opportunities to report symptoms in the second interview. Item (b), failure to exclude acute disorders, could very well have occurred, because we had not anticipated the use of this panel when the survey was first taken.

A second set of reasons might be those based on a respondent's bias and, although I do not have very good figures on this, I feel somewhat strongly about it based upon my own observations. In the first place, several incidents that occurred led us to suppose that respondents felt that repeated inquiry by Health Department personnel about symptoms of cough and sputum is related to a suspicion by the Department's personnel that the respondent has tuberculosis. I think that this might be a very substantial bias which would occur in this Country and not be quite as great a handicap in Great Britain, for example. Secondly, if the interview occurs during a remission, the subject may have forgotten the previous condition, and this is a source of bias. Third, among other reasons for under-reporting, might be that this is the way the subject used to refuse to be interviewed. Finally, we must also consider the possibility that a true change in symptom occurs. Until we can collect more adequate information about methodologic aspects of this, I think we must assume that this could occur.

Refusals were few. We made one other observation that is of interest. In the second interview, which followed closely upon the private physician questionnaire, five of the twelve refusals were apparently connected with the physician's attitude as communicated to the panel member, and as recorded by the interviewer. In each case later personal contact with the physician involved led to a favorable support of the method and purposes of this survey.

In conclusion, I would like to say that repeated interview of symptomatic individuals who are detected from a population survey seems to be a workable way of studying chronic disease. But, under these circumstances, the research design must anticipate that individuals, once classified into categories based on symptomatic responses, may not remain permanently in this same category.

DR. KORNS: This gives me the impression of being a rather sophisticated study, and that the men doing the work are aware of many of the pitfalls and hopefully are going to avoid them as they pursue the project during the coming year. This business, again, of lumping together a group of symptoms leaves me a little "unhappy." I presume that is inevitable because of the nature of the entitites being looked for. I did not hear you refer to how you defined "chronic" versus "acute."

This seemed to be an element that might have given rise to the different response on the two interviews. What sort of definitions did you apply?

The slight change in the schedule used in the second interview, I suppose, would have led to more positive responses; although I wonder if you are certain of that. Could it have done the reverse? Is there another possible element producing the difference that you observed? For what time interval does the interviewee report that illness occurred? Is this for illness at the time of inquiry? Within a day? Or within some other specified period?

DR. GOLDSMITH: You will see in the middle of the right-hand page of the "schedule" that the inquiry was made about the behavior with respect to this disease (listed) for the previous two weeks. We consider this period of some validity. We also inquired concerning the previous three months; but, we used this latter period as a control of the previously collected data, and we don't think it likely to have a great deal of validity.

The differentiation from chronic to acute: I believe that some place in one of my manuscripts I deleted the word "acute" and put "persistent." I think, under the circumstances this is about the only definition that is workable. It is purely an operational definition. It is very easy to interview people and not get any evidence that they have an acute illness; but, at the same time, to get positive evidence of the current presence of a symptom and that, I think, was the problem that I wanted to refer to. We just could not be sure that a lot of these people did not have a "cold," failed to report it as an acute episode but did report that they had a cough. In fact, we found that a number of these things did occur.

I am not any happier than anyone else about lumping together symptoms, particularly about lumping symptoms and lumping "diagnoses" of bronchitis or asthma. I think that in an interview situation my own conviction is that it is far better to use a term that is likely to be used homogeneously within a population and in this sense I would use, with the possible exception of asthma, cough and sputum alone, and dyspnea. Even so, it is a very difficult matter. But I believe I would exclude the term "bronchitis." Its occurrence in my title was not of my election.

DR. CIOCCO: I think that there is another point about this study which is very important for us to keep in mind. Whenever we do follow-up studies -- and we are going to do many, many of them, in trying to learn something about chronic disease -- we are going to run into these kinds of problems. We really don't know how to handle them analytically. For example, in your first table, Dr. Goldsmith, you will find that you show a high mortality among those who had cough.

DR. GOLDSMITH: That's right.

DR. CIOCCO: Now, that brings up a question: what does it mean?

In your Table No. II you find a relatively high mortality among the individuals that you didn't see in the first interview. What does this mean? What do you do about it in the analysis? Well, these are some of the questions which arise as you conduct a study such as this.

The fact that the individuals do not respond in the same fashion on repeated observation has been brought out many times. I know we have brought it out, when we resurveyed Hagerstown after twenty years. One of the things that we learned from that resurvey was that if the condition is mild, it is very apt to be forgotten. If it is severe, it is more apt not to be forgotten.

I think we ought to consider studies, such as the one that Dr. Goldsmith has reported, primarily as a contribution to methodology. However, I am still curious about one point, and it is the only question I would like to ask you, Dr. Goldsmith. It is: How are you going to measure the effect or relationship of air pollution to the conditions studied?

DR. GOLDSMITH: With respect to the mortality, I think it is of interest that two of them appear to have died of pulmonary embolism; two of predominantly arteriosclerotic heart disease, or coronary heart disease, or a stroke, or something in this category; and two in accidents. This is my best recollection. Certainly the small numbers do not lead us to think that the mortality breakdown is significant. We obtained the death certificates and we plan to continue to do this for the people in our sample who die.

The question of measuring the effect of air pollution is a very difficult one. We have to make the assumption that people who live, in an area of Los Angeles County with high air pollution should have an experience whose seasonal distribution of sickness is greater. During air pollution periods they should have an exacerbation. This is all, of course, assuming that air pollution continues to bother Los Angeles. Of course, it does vary from year to year, which is one of the "bugaboos" of an epidemiologic survey.

I might make just one comment concerning our present thinking as to methods. We anticipate that with the next interview we will be able to have our interviewers trained to do some simple pulmonary function measurements on a door-to-door basis. At least we are hopeful that this will work out. If it will, I think we will have added another dimension to this type of study.

DR. WRIGHT: This interview is quite in the nature of taking a history, and I suggest that it falls into an error. I wonder what your thought is. You ask the patient, to make a statement about his own diagnosis before he tells you what his symptoms are. You ask him, "Do you have bronchitis?" and, "Do you have asthma?" Then you proceed to ask the questions that might substantiate it. Well, this forces him virtually to support or deny his first reply. Later on in your form you say, "Are you more short of breath than other people of your age?" Then you ask him for the supporting information. "Do you have to walk slower than people of your own age on the level ground?" I would suggest that you turn these around and ask for the information that would lead you to some knowledge. Then, at the end, let him say what he thinks is wrong with him. This is a common error. It is a great problem in every doctor's office. The patient, before he comes in, has some idea of what he has, states what he has, and then proceeds to justify it.

DR. MANCUSO: We will start off this afternoon with "A Study Of The Health Effects Of Urban Air Pollution - Methodologic Approach: Preliminary Report," by Dr. Louis Zeidberg.

DR. ZEIDBERG: We have devised a study plan as part of a contract with the Air Pollution Medical Program of the Public Health Service which asked us to do so primarily for the purpose of establishing a method of study.

It was recognized that the air pollution problem in Nashville is not too acute. Nevertheless, it is a different kind of air pollution than is found on the west coast. Predominantly, our problem has to do with a true smog -- a combination of coal smoke and fog. We set up as the main objective of our study to do general morbidity surveys of Nashville and some of its surrounding area for the purpose of establishing general and specific morbidity data. The second objective was to relate these morbidity data to air pollution, if possible. The third objective was to provide, thereby, some socio-economic and medical data concerning the people in the community, that might be useful to the local health and welfare agencies in their planning needed services.

The program was predicated upon the provision of adequate aerometric studies to be provided by the Sanitary Engineering Center of the Public Health Service. We anticipate the aerometric studies will begin perhaps within a month or so, and that they will involve the most comprehensive plans for covering such an area that has ever been done anywhere. It is planned that the aerometric stations will be set up for certain types of analyses at half-mile intervals throughout the city. There will be some 120 such stations, with more complete measuring stations scattered at intervals in that area.

The morbidity survey is planned in two phases. For the first phase we expect to do about 3,000 households, which will comprise about five percent of the households in the area. The very thin outline on the map shown in the first slide, shows the area of Davidson County in which Nashville is located. The heavier outlines represent "communities" as they have been established by the Nashville City Planning Commission. These "communities" comprise arbitrary areas based on 12 different criteria, some of which are socio-economic, others ethnic, and still others geographic. The objective of the City Planning Commission was to establish areas that had a certain degree of homogeneity of population for its broad planning purposes.

Within these larger "communities" there are subdivisions that are called "planning units." We decided that we would use this breakdown of the Nashville and suburban area, rather than the traditional census tracts, for two reasons: One is that the City Planning Commission believes that its arbitrary arrangement of areas is more realistic than the census tracts. Our university sociologist is not so sure of this. The second factor is that the data on which this arbitrary breakdown is dependent are not older than six months, whereas, the data for the census tracts are now some eight years old. So, for the purposes of our scheme for the morbidity survey we are better off having these up-to-date data concerning the number of dwelling units located in various parts of the city.

By taking all of the "communities" within the city, and some portion of most of these "communities" and "planning units" in the suburban areas we will eventually have between 60 and 70-thousand households. By a plan of stratification we shall select about ten percent of that population and about half that will be surveyed in the first phase of the study. After these data will have been given a quick review, we hope to have sufficient information to make more precise the second phase of the study. For that second phase we hope to know enough to select certain areas that would be likely to yield the most profitable information.

The stratification will go from "community" to "planning unit," to "block," to "dwelling," and, finally to "dwelling unit." We are most fortunate to have quite complete block by block data in Nashville that were compiled by the City Planning Commission. These data are six months old at the worst.

We devised and tested a questionnaire in the field. The field test occurred during part of the summer of 1957 and was conducted by graduate students in the Sociology Department of Vanderbilt University under the direction of the Head of the Department, who has had a very good background in surveys. His training background includes a period of time with the National Opinion Research Center of Chicago. We have leaned very heavily on the sociologists in devising our questionnaire, and have finally come up with one which we presented at an epidemiology conference back in December. It was not accepted unanimously, to be sure. I think every epidemiologist present had some little something he wanted to add to it. I am afraid we will not be able to accomodate everybody because of the time it would take.

The questionnaire that we have finally come down to has eliminated some desirable questions that we had originally, during the trial period; but, we have sacrificed some of what some people deemed to be essential information for the advantage that will accrue from having a shorter questionnaire. We believe that the longer the questionnaire is, the greater is the chance of getting "diminishing returns." It doesn't make any difference how much data you collect if these data are unreliable. We would rather have a smaller, compact questionnaire, with more reliable data that we can handle.

Our questionnaire is divided into sections. First, there is a section on the medical data. We asked specifically about illness concerning every member of the household, preferably selecting for the respondent the female head of the household. The data asked for concerned illness on the day of the interview, during the previous week, and during the previous year. We go on to ask specific questions concerning specific diseases, grouped according to organ and system. For example, in the cardiac group, we ask: "Have you, or has any member of your family, ever had rheumatic heart diseases or high blood pressure, etc.?" -- and go down the list of such diseases. We then wind up by saying: "Have you, or has anybody in your family, ever had any heart trouble?" -- or " any other heart trouble," if they have already responded that somebody did have something.

Every time we get an affirmative response, we complete a special form which details the information, and we seek to determine whether this has been a medically attended illness, or if it is purely a subjective diagnosis. We are expecting to obtain authorization from people to consult their clinic or hospital or doctor, in order to authenticate the information that they give us. I don't think that we will be able to do this in every case, but I hope we will be able to do it in a fair-sized sample. It will tell us just how reliable is the information we are obtaining from our respondents.

In addition to the medical data we also have a fair body of information concerning the socio-economic status of the individual and of the family; a residence history; and an occupational history for all occupied individuals. In the data analysis we are expecting to be able to correlate the data that we ourselves obtain, with the aerometric data which will be supplied to us.

Our plan is to complete the first phase of 3,000 households in about a month. At that rate we expect that there will be some 100 families interviewed on any given day. That will comprise some 350 individuals. According to where those people live, and according to the aerometric data that are provided for us for that given day for that given locality, we may be able to determine the association of that day's morbidity with the air pollution data. We expect also to be able to do this for the diseases of longer duration, as we get information about all the other diseases, and as we consider as well the residence and occupational history.

We do not have any illusions about how reliable our data are going to be. We know from the experiences that Dr. Thompson had in Donora, and that others have had, that if you compare the information you pick up purely on a questionnaire with the information you pick up by examination of the individuals, there is a wide discrepancy between the reported illness and the actual illness. We do not have any illusions about that. We hope to pick up a certain amount by referring to the doctor or the clinic or the hospital.

I think the chief advantage of our plan will not be that it establishes absolute morbidity rates. Rather its use will be to tell us about relative morbidity rates, that we could then compare for people living in two different areas, one that is perhaps not polluted and another area that is heavily polluted. We expect, perhaps, to be able to establish at least a suspicion of "guilt by association." However reprehensible this may be to other disciplines, to the epidemiologist I think it is valuable because it may give him some clues as to how to proceed and what to look for. We are, after all, groping blindly.

Dr. John Gordon has pointed out that in air pollution studies we don't have a disease and we don't have an agent. That sort of situation should be most discouraging to any epidemiologist. But we hope, by pursuing this kind of approach, to get some clues as to how to proceed further; what to look for. I think, perhaps, that in the last analysis that is about the best that we can say for our approach other than to establish some methodology.

DR. KORNS: In many ways the questions that come to mind with respect to this study are comparable to those that we have raised in prior discussion. I hope that the lessons of Detroit are going to be heeded and that these errors are going to be avoided.

I am a little unhappy about using a schedule of questions that attempts to elicit from the respondent in the home whether or not individuals in the family have a certain disease entity. The schedule has a number of questions that require a fair amount of medical sophistication on the part of the respondent. It would seem more sensible, to me, to ask the respondent in the home what symptoms he has had rather than what disease since these are the terms in which the average layman speaks.

I am a little worried that since most morbidity is inversely related to education and socio-economic status, and since geographic location of residence is often so related as well, and since the place of residence, may in turn, be related to air pollution, that by collecting morbidity data on the basis of the respondent's reply to a question, "Do you have such-and-such a disease?" or "Does someone in your family have it?", rather than on a symptom basis, which the patient would better understand, you might introduce an element of bias that might produce a spurious association.

You indicated that it takes more time to get the information by asking them questions on symptoms rather than disease categories; but, it may be worth the extra time to do the former. It might be well to rotate interviewers too. This may have occurred to you. Interviewers that are assigned solely to a given area of, say, high air pollution might be more or less zealous in uncovering evidence of morbidity and thus might introduce an element of bias. To correct for this, interviewers ought to be shifted periodically to other areas.

The City Planning Commission Survey of six months ago is a wonderful thing to have. I notice that they define their areas on the basis of some 12 characteristics, as you mentioned. However, am I right, Dr. Zeidberg, that the requirement is merely that one or more characteristics be comparable in these areas? I would hope that more than one characteristic would be comparable, and I suppose actually this is so. On the other hand, wouldn't it be well to make certain of this.

The proposed study design looks solid. It is going to require tremendous labor and application. I believe you have other auxilliary projects that you are introducing into the core study -- the following up of a group of specific disease patients, to see how they also fluctuate clinically with elements of air pollution, etc. I admire your courage, and wish you luck.

DR. WENTWORTH: I was one of the epidemiologists to whom Dr. Zeidberg referred who wanted a lot of impossible things in his form. It occurred to some of us before, and it occurs to me again, that Dr. Zeidberg did not go into a complete discussion of the gathering of the environmental data. As it was presented to us now it is very comprehensive plan. I think that when one compares the manner of getting the morbidity data with the completeness of the manner of collecting the environmental data, the plan for the morbidity data looks pretty "puny".

I just wonder about the approach of trying to gather data on the pre-existence of chronic disease by the interview method without using more effort at medical confirmation. It is the same criticism that can be made of the other studies. One wonders what "bronchitis" is. And I know that it may be an unfair worry, but it seems every one who comments on this begins by saying, "This worries me a little." Can't we do something about it to try to get some medical confirmations, rather than to take the people's word for it?

DR. MENEELY: As many of you know, Dr. Zeidberg and I are closely associated; and, yet, I have no role in his program. We are physically located close to each other, having adjacent offices; but, I am an internist and not in the field of public health and epidemiology.

But, apropos of some of the comments that have been made on some of the epidemiological studies, let's consider the difference between asking a patient who has tuberculosis a series of questions, as a clinician does, designed to determine whether the patient is going toward or away from a state of health. This is a very subtle sort of business, and those of you working in the TB field are aware of the great difficulty of spotting whether a patient with tuberculosis is going toward or away from good health. But it certainly is a simple enough matter, ordinarily, to make a distinction between whether a person has or has not got tuberculosis. In other words, if a person has active tuberculosis, it is an identifiable disease; and, if it has been diagnosed, he usually knows it.

So, it seems to me that there are levels of organization in one's thinking about this. To say that one should get at disease by symptoms implies really, then, that one should take an unbiased medical history, an amibitious hour and a half undertaking in the hands of a skilled person.

DR. GOLDSMITH: It seems to me, first, that we have a large number of criteria upon which we base the diagnosis of a disease, whether it be bronchitis or pulmonary tuberculosis. As a clinician, I think most of these are extremely uncertain. It is with some experience and with the knowledge as to how to combine findings and knowing with what sort of people you are talking, that they may become reliable tools. I know of several attempts to validate diagnostic data obtained by physician interviews and patient interviews. Much of this was done in California by Dr. Breslow, long before I got there. I think it is unfair to state, as I think has been stated, that epidemiologic methods are in a wholly different realm of accuracy from clinical ones.

I think that if one defines unambiguously what one is trying to measure, and if one consistently uses the same method of defining it, that he can probably come just about as well at getting the sort of reproducibility from a good epidemiologic study as he can from some clinical studies. It depends a great deal on what the condition is that is being studied. But I think it is quite unfair to imply that all epidemiologic studies, *ipso facto*, are going to be inaccurate because they are not accompanied by a careful history, physical examination and laboratory review.

DR. MANCUSO: I think Dr. Goldsmith has really started something. I hope we have enough time to take care of that.

DR. FREDRICK: I am going to join the defense. The medical consultants connected with our study went over this matter of medical examinations for a long time and concluded that it would not contribute anything. It would provide us data that would be just as far away from the fact as by having the person say, simply, "My head hurts."

I want to call your attention again to the Cornell Medical Index that we used in the Detroit study. It appears to be a useful tool. It was originally designed for a different purpose. During theWar it was used as a substitute for a physical examination when hiring workers. It seemed to work out all right. It is easy to use in a program of this type involving community health studies.

DR. CIOCCO: I cannot keep out of this argument, from a non-medical point of view. I do not see any good reason why one should defend one approach or the other. We should, in fact, recognize the limitation of, let's say, the interview method.

In a study which Dr. Thompson reported we have shown the number of persons with heart disease. I think that unless we would assume that such underestimate is unbiased, it is going to have some effect on our attempts at making valid associations.

The point I want to reemphasize is that we ought to try for accuracy. We cannot do so in this case because it would cost too much; and, maybe, it is not even good enough. We don't have tests to use by going about and examining people. But let's not say that we are going to get just as good results without examinations. We are not going to get just as good results. But, at least let us recognize the errors and, as we go along in these studies, hope to eliminate them.

DR. ZEIDBERG: Dr. Korns has raised the question of symptoms of disease, as opposed to disease. There we are always faced with the problem of how you are going to interpret symptoms. This is something I said at another meeting at which some of you were present. I hope you will forgive me if I repeat for I think it might bear repetition.

We have been urged, for example, to include among a few symptoms the symptom of "shortness-of-breath." I raise the question of what does this mean. You get "shortness of breath" with heart disease. You get it with pulmonary disease. You get it with obesity. You get it with anemia. You get it with bronchial asthma. You get it with passion. So, where are you, when you try to interpret this thing? After all, we are going to be using lay interviewers, and these people will not have the background to interpret symptoms and to pursue them any further.

The other question that Dr. Korns raised was the use of specific medical terms, certain terms like "nephritis". I don't think we have used "nephritis". I think we used "kidney disease" in our questionnaire. But we did, however, use other terms that were "worse", like "bronchiectasis". Our feeling is that if a person knows he has "bronchiectasis", he has it. If he doesn't know what it may be, the interviewer can describe it to him a little bit, and ask him about that. Our interviewers were actually briefed in the symptomatology and meaning of certain of these medical terms that we were throwing at the respondents.

I would like to assure Dr. Korns that this morbidity survey is not the only one that we have in mind for the community. We have three others, one of which is a one-year study of people with known cardiorespiratory disease. I did not bring that up, for lack of time. I thought we might devote our time to the morbidity survey. I would also like to point out that what he calls courage on our part in undertaking this survey may be pure ignorance.

To Dr. Wentworth I want to say, thank you for the kind words. I will, however, point out to him that we are hoping to get as much medical confirmation as we can, in order to try to overcome the alleged and, perhaps real, "puniness" of the medical data, compared to the other. I think another factor of importance is that in one sense, it perhaps makes little difference how much illness there actually is in a community. I think -- what is more important -- not from the air pollution standpoint, but from the standpoint of medical and welfare agencies -- is how much illness people think they have. If we can uncover that, we will at least be having some ancillary information.

DR. MANCUSO: Thank you. We would like to introduce another report on the program, one that is not listed. I know that Dr. Thompson is here from the University of Pittsburgh, Graduate School of Public Health, and I would like to ask him to tell us about the Donora follow-up study that he has been making and that we have heard so much about.

**DR. THOMPSON:** Nine years ago, last December, the Public Health Service conducted a study in Donora, Pennsylvania following the episode that occurred there. At that time a sample of one-third of all the persons resident in the borough was questioned concerning the symptoms that they had during the week of the episode. On the basis of this questioning, and the medical care that was received, Dr. Heimann, in reporting the data of the studies, classified these people as being "not affected" or "affected" and further graded the "affected" by degree as "mild", "moderate" and "severe."

We went to Donora last February eight and a half years after the episode and again questioned the residents who were still there. We asked them what had happened to various aspects of their health and what kinds of medical care they had utilized in the interim, since that period of eight and a half years ago. We also obtained information on mortality.

Of the 4,095 persons who were surveyed in 1948, we were able to ascertain the survivorship of all but 41 people. We also interviewed, either personally or by mail, 95 percent of the original group. We obtained death certificates on the 320 persons that had died since 1948.

I might emphasize that our interviewing was done by lay interviewers who were not aware of the background history of the persons who were being questioned -- that is, how they had been classed as having responded during the week of the smog in 1948. Furthermore, most of the people who were questioned did not know how they had been classified. Further, they had forgotten how they had reacted during the 1948 episode. So that in a sense, the questioning done in 1957 was "blind questioning."

The results are very interesting. I would not like to interpret them just now. I can tell you what we found. There is a general difference between the "affected" and the "not-affected" groups, both in regard to mortality and to morbidity. There is a clear distinction between the survivorship of the two groups. The "affected" group survived at a lower rate than the "not-affected."

If the 320 deaths are classified by age, sex, and a few other pertinent factors, it becomes very difficult to say anything about particular causes of death that might be high or low in the two groups.

In regard to morbidity there is again a clear and marked distinction between the "affected" and the "not-affected" group, all the way across the board. The prevalence of the cardio-respiratory diseases today is higher among the "affected" group than among the "not-affected." The incidence of these diseases, as reported on interview, again shows that the "affected" group has had a higher incidence than the "non-affected" group.

**DR. MANCUSO:** Thank you, Dr. Thompson. Now we will go on to the presentation, the "Index of Air Pollution Correlated with Mortality", by Nicholas E. Manos of the Air Pollution Medical Program of the Public Health Service.

**MR. MANOS:** This is an effort to do the best we can with the tools we have available to us right now in an area which we think is worth a gamble. In order to correlate mortality and morbidity with the degree of air pollution, as it varies from city to city, we need an index of air pollution. Air sampling at the present time is a comparatively new technique and has many limitations. So, in order to do such a study, it is essential that we use available data which would reflect the sources of air pollution.

The index that we shall discuss has been developed for the 163 metropolitan areas in this Country. It includes all cities of 50,000 or more population. The index is based on the three main sources of air pollution, namely, home-heating, industry and automobile exhausts. It is, therefore, a source index.

Our project is not limited to the development of a single final index for ranking cities in terms of air pollution. It is designed for the study of the relationship of many different measures of air pollution to many different causes of mortality. What we call an index is, therefore, not really a single index but a series of indexes, each of which is to be correlated with mortality. In this manner, it is our hope to identify sources of air pollution which have the highest correlation with certain kinds of mortality. The ultimate hope, here, is that we might lend supporting evidence to other studies in pointing out areas which should be studied more intensively. I may say, parenthetically, that the approach is not that of a designed study. We have a broad plan, but the approach is rather one of successive approximations. We start somewhere and as we move, we keep refining, so that we are not committed to any rigid plan in advance.

In our first group of correlations, in which we used 50 causes of death we related these 50 causes to a series of indexes and we found that the highest correlations were concentrated in five cause groups. I stress that this is just the "first look" at the results. Most of the 50 causes showed very low correlations. The four cause groups of mortality which stood out were lung cancer, cancer of stomach and esophagus together, two heart disease categories and motor vehicle accidents. The high correlation between death from automobile accidents and our indexes of air pollution was a negative one, whereas the others were positive. Thus, we encountered what we knew in advance would be a major problem; that is, the disentanglement of the relationship of mortality and air pollution from the relationship of mortality and many factors other than pollution. These interrelationships make it necessary to quantitate the obviously well-known, and better known, associations of mortality with these other factors before proceeding further with the relationship of air pollution to mortality. We hope to study, first, these other relationships which is not, of course, our primary goal. Then we may use such relationships as a basis for trying to explain the deviations that do not fit the relationship, and to see whether they correlate with air pollution.

If the main purpose of the project, which is the indication of a relationship between health effects and air pollution is not successful from this study, we feel that results from this project will at least reveal new information about the geographic variation in mortality. We would, at least, be getting some background information that might be useful to workers in the fields of air pollution and environmental health.

I cannot go into specific findings at this time, because we have just started the analysis. I shall describe the method briefly. It consists of constructing various indexes of air pollution based on source data. The different types of industrial sources are measured by the number of employees in each type of industry as provided to us by the Bureau of the Census. We prepared many systems of "weights" for the Census Bureau, which they used to construct the various types of indexes on their UNIVAC. The weights, incidentally, would vary so as to give different industries different degree of emphasis, to see what happens to their correlation with mortality as we vary the emphasis.

As a measure of general industrialization we use the simple figure of percent of the employed population engaged in manufacturing. As a measure of general characteristics of cities we use such factors as population density and median income. For home-heating data we have the number of heating units for the four main sources, coal, gas, liquid fuel and wood. As a measure of motor exhausts we use data on gasoline service station sales, which is a homogeneously compiled figure from city to city.

Our first step in the analysis was to prepare simple linear correlations of each of these indexes with each cause of mortality for various age-race-sex breakdowns. We then studied these to see which causes correlated best. As I say, we found that there were four with positive conditions that stood out; so, we will now concentrate on pursuing that finding.

When analysis of these linear correlations is completed, we will go to multiple correlations, correlating more than two of these indexes at a time with mortality.

Some of the unique features of this project are: first, the planned construction of indexes based on a priori knowledge or opinion. We used, for example, the opinion of workers in industrial hygiene to rank the industries in order of suspicion. Then we used various techniques to check their opinions, such as reversing their opinions or modifying them in such a way that if their opinion was valid, a modification to make it worse should make the correlation with mortality worse.

In the multiple correlation we will use a similar technique by using three indexes together and keeping two of them fixed and then varying the third one in such a manner that should make the correlations better or worse if the index is really related to air pollution health effects. Then we see whether it really behaves as expected. These are valid techniques for this particular field in which so little is known. They provide us one of the best measures for possible significance in this type of very preliminary pilot research.

Only one cause has so far behaved according to the expected pattern. This was lung cancer. In the four causes that have high correlations, the correlations do not vary in the same manner. They vary in ways which lead us to believe that there is something significant there. It may, of course, turn out not to be air pollution.

If we are successful in what we are doing, we hope to have a useful index for ranking cities in terms of air pollution so that we can select cities for intensive community health studies. We are also after clues as to the sources of air pollution that affect health. We start out with broad categories of industries and groups of air pollution sources on which we can concentrate later if we find clues pointing to them by this approach.

DR. CIOCCO: This is the type of study that many of us interested in statistics feel ought to be done. Generally, we say, "let someone else do it." Obviously, he is going to find some variation. He has found some variation in mortality pattern by communities. He is going to compare those variations. He is going to see what relationship those variations have to a variety of indices, some of which are probably good, and some of which are bad or indifferent. And, out of that perhaps we will get some clues as to what to do next. I think it is a most useful type of study. Perhaps it may not be as productive as some of us would hope. Nevertheless, unless one does it, we will never know.

I would raise a question, however, as to the use of the term "correlation", and the particular term "multiple correlation." Are you really planning to do that, or are you just using the term in a general way? If you are planning to use multiple correlations of one kind or another, I have an idea, perhaps, that there will be great hazards of interpretation, particularly since you are dealing with such complex things as the types of indices that you have developed.

DR. MANCUSO: I want to thank all of you who have participated. I will now turn the meeting back to Dr. Heimann.

DR. HEIMANN: Thank you very much, Dr. Mancuso, the meeting is adjourned for the day.

**DR. HEIMANN**: The purpose of our session this morning is for the medical panels to summarize for themselves and for the non-medical panels what was covered in their discussions. The reviews will be given by the panel chairman of each of the panels that we had in the pas two days. The chairmen have agreed that if you have any questions you would like to ask, or any comments you would like to make, you may do so.

The chairman of Panel #1 which was entitled, "The Effects Of Air Pollutants Upon Enzyme Systems, Cell Cultures And Tissues," will now make his report. Dr. Hayes of the Communicable Disease Center of the Public Health Service was the chairman of that panel.

**DR. HAYES**: As I understand it, our chief function this morning is to give you the highlights of our discussions - highlights that you may be able to use in some discipline other than medicine. Therefore, my summaries are going to be extremely brief.

In our panel on The Effects Of Air Pollutants Upon Enzyme Systems, Cell Cultures And Tissues, we were concerned with attempts to determine how air pollutants may cause injury. Some poisons are known to be about equally harmful to all kinds of cells, and their action can be studied by using, for example, bacteria or isolated tissues or cells taken from the body and grown on special media. Other poisons have little effect on isolated cells; rather, they have their chief effects through interference with the nervous system, or some other complex function, which is manifest only in the intact animal and can be studied only in the intact animal. Perhaps the latter materials could be studied if one could isolate nerve cells and elicit some evidence of nervous activity from them in tissue culture.

We heard two reports about the effects of pollutants on cells. The first was by Drs. Gast and Estes and concerned the exploration of the effect on bacterial and other cells of synthetic air pollution of the Los Angeles type. The concentrations of pollutants used were greater than those which are found in the ambient air. It was shown that such smog when irradiated has greatly increased ability to reduce growth and respiration in such systems.

The second report was by Dr. Pace. It was concerned with the effect of sulfur dioxide and nitrous oxide, and some salts of these gases, on cells from rats and from man. The studies showed that, of the two gases, sulfur dioxide is more harmful to cells. This, of course, does not mean that nitrous oxide is not important through its effect on the intact animal or, especially, through interaction with other materials in smog.

The third paper, presented by Dr. Mountain, had a very different approach. Two lung tissue enzymes of rats and rabbits were studied after the animals had been exposed in different ways to ozone inhalation. Ozone is interesting in several ways. It promotes chemical change in other materials present in smog; and, in spite of its being very poisonous, animals quickly develop some tolerance to its acute effects. Dr. Mountain found that the activity of lung alkaline phosphatase is greatly reduced and the activity of 5-nucleotidase is somewhat reduced when the animals are exposed to ozone. However, this reduction is not as great in rats that have been made tolerant by previous exposure to the gas. Not only is alkaline phosphatase activity lost from the lung, but that portion of the enzyme system which is activated by magnesium ions is increased in the blood. The change occurs in half an hour and continues for two or more days after exposure to ozone.

The test has been positive when applied to men who had had occupational exposure to a mixture of carbon tetrachloride and carbon disulphide used as a fumigant. Thus, through this basic study, a test has been found which may be of very practical use for measuring the effect of one or more kinds of air pollution on man.

DR. WEICKMANN: In the last report that you mentioned, what was the ozone concentration which was used?

DR. HAYES: Is Dr. Mountain here to reply?

DR. MOUNTAIN: In the rabbits, in which we found the changes in the circulating blood, we used a concentration of ten parts per million of ozone. The time of exposure to that concentration was one hour. In the studies of lung-contained enzymes, we used two levels of ozone concentration. We used 16 and six parts per million and found significant changes in the enzyme content of lung tissue for both concentrations.

DR. HAYES: If there are no other questions, I shall return the meeting to Dr. Heimann.

DR. HEIMANN: The next panel was entitled "The Effects Of Air Pollutants Upon Man And The Intact Animal Under Experimental Conditions". Dr. Harold Hodge was the panel chairman. Since he had to leave our meeting early, Dr. Emik, the secretary of the panel agreed to review the panel discussions for us.

DR. EMIK: The title of this panel is not exactly accurate. There was nothing reported on man. There were five papers on various aspects involving the intact animal. One of these happened to consider the intact animal as well as the "intact" air, as produced by the efforts of man in the Los Angeles Basin. This was, in general, a report of Dr. Catcott's activities in the Los Angeles Basin.

He started without any idea of what the possible effects on livestock, domestic pets, or other animal populations in the basin might be. He was informed early of reports of effects on pets and parakeets, and a more definitive report that chickens within the more polluted areas had been adversely affected in growth and egg production. From this standing start he investigated the very meager statistics on poultry and cattle diseases and found nothing inconsistent with the standard endemic seasonal incidences of disease. He went from there to talking to the veterinarians and eventually sent questionnaires to all of the veterinary practitioners. This elicited the general opinion that about a third of them considered that there was some adverse effect during bouts of high pollution on the eyes and respiratory systems, principally of dogs.

He was then able to establish two field studies, one on dogs and one on chicks. The dogs were selected from relatively high and low pollution areas. Twenty-five were collected from each of these areas and their respiratory tracts were examined pathologically. These were completely negative.

The chick experiment used a select genetic strain, one of the better controlled animals that have been used in experimentation. One hatch of 200 chicks was split into two groups. One group was placed in relatively high pollution in Arcadia, the other in a cleaner area in Ontario. The principal difference which could be measured was that there was a 20 degree temperature differential, the hotter temperature occurring in Ontario. Over a three-month period these chicks showed no apparent changes except that the ones in Ontario grew a bit slower than the ones in Arcadia. Once a week two from each location were autopsided and examined. The histological findings from these chickens produced nothing exciting at all. One of the items of possible interest was that these chicks in the hot temperature had to eat about a fifth more feed, although they gained less weight.

The second paper of our panel was that reported by Dr. Brieger. Using a chemically inert, insoluble dye in 2-micron and 6-micron sized dusts on rats, he determined the distributional fates of the dust at different points after exposure. Initially the major proportion was found on the skin. After a day the skin level dropped to less than half, and the gastrointestinal tract content increased to approximately half. The remaining portion was found in the lung. After a week, around 80 percent of the measurable dye was in the lungs. With intratracheal injection of the dust, it was determined that approximately 23 percent of the intratrachel injection could be recovered in the gastrointestinal tract. Supporting evidence was quoted by Dr. Krackow.

The third paper was largely a report of developmental problems and state of progress. Dr. Bryan at UCLA is underway on an experiment to determine the effects of a hexene-ozone-$NO_2$ mixture on mice exposed to Diplococcus pneumoniae.

Dr. Stokinger has recently completed some preliminary studies on the effects of oil mist aerosols, in conjunction with ozone exposure, on rats and mice, using approximately four parts per million of ozone as the insult and 400 milligrams per cubic meter of oil as a mist of one micron size. In the contemporaneous exposure to ozone and oil mist no particular effect could be attributed to the oil. When he split these by time relations, he discovered, by delaying the ozone exposure until six hours after the oil exposure, there was an enhanced mortality.

Dr. Deichmann reported on his nitro-olefin work. He synthesized many of the products he was using. He has synthesized around nine or ten, varying from 2-nitro-2butene up to the nonene. The central feature of these compounds is the double carbon bond in the aliphatic chain, and the $NO_2$ on the carbon atom which has a double bond. These compounds produce a marked and severe effect at the acute level of experimental exposures. He has used them on chicks, rabbits and rats. The general effects are similar for the different compounds, but a little more marked in the shorter chains.

One of the striking things that he reported, not officially here, was the marked pain response of these animals. They cry out to the best of their ability, upon these extreme exposures. They try, in whatever manner they can, to avoid the exposure. In comparisons between high and low humidities in his two chambers, there was a marked difference, and a high amount of edema and fluid in the pleural cavity, when these were administered under a high humidity. Otherwise, the general features observed were those of a severe insult which consisted of both circulatory and respiratory distress and failure. These materials give marked eye irritation in man. I had this demonstrated to me while I was at the laboratory. We all seem to feel that the eye response is very similar to the type of eye irritation which one experiences under Los Angeles smog condition.

DR. GOETZ: What was the size range of the oil mists that were used?

DR. STOKINGER: They had a mass median diameter of one micron. There were no particles below three-tenths microns, and they had standard geometric deviation of 1.6.

DR. GOETZ: That size is large.

DR. STOKINGER: We realize that.

DR. HEIMANN: Panel III was entitled "The Effects Of Air Pollutants Upon Lung Function." Dr. Nelson of New York University was chairman of that panel. Dr. Nelson, would you tell us what happened during your session?

DR. NELSON: The panel that I will attempt to summarize briefly was made up of four presentations. There was to be a fifth one, but unfortunately, it had to be omitted.

The papers covered the general problem of the assessment of pulmonary function as a means of appraising the effects of inhaled irritant air pollutants on either animals or man. Of the four papers, two came from the Harvard School of Public Health and two from the University of Cincinnati.

The first paper, presented by Dr. Whittenberger, had a last-minute change in title. The title was changed from "A Study Of The Effects Upon Lung Function Of Man Of Controlled Exposure To Irritant Air Pollutants," to "Methods For Study Of The Effects Upon Lung Function Of Man Of Controlled Exposure To Irritant Air Pollutants." The change was prompted by the difficulties which they encountered in dealing with the problems of legal liability in experimentally exposing men to known toxic materials. Accordingly, there were delays in getting their study underway. Dr. Whittenberger informed the group that the liability problem has now been resolved, he believes, in a satisfactory way, and the work will be able to proceed.

Dr. Whittenberger then took the opportunity to describe a new device which has been developed by Dr. Clements for a simplified measurement of pulmonary expiratory resistance.

Pulmonary expiratory resistance, is believed, by many, to be a most sensitive way of measuring the lung response to irritant gases and aerosols. The procedures used in the past have been rather complicated and difficult to apply either to large numbers of subjects or to the field.

The procedure which he described represents a considerable simplification so that it can be employed in field studies. Dr. Whittenberger's group has examined it in the laboratory against conventional procedures and they believe that it is essentially a reliable procedure and promises to be of considerable utility. However, he pointed out that it had certain limitations, and then proceeded to give us a graphic demonstration of one of these limitations, by attempting to demonstrate its use. The limitation that he pointed out as being present prevented the successful demonstration of the machine at this time. They believe that this defect is correctable. In short, this promises to be a thoroughly useful device.

The next paper dealt, not with human responses, but with animal responses, and was by Dr. Amdur of the Harvard School of Public Health. Dr. Amdur reported newer work on the measurement of pulmonary resistance and pulmonary compliance -- particularly changes in pulmonary resistance -- in the guinea pigs, using the very ingenious procedures that she has developed. She was able to reaffirm her earlier observations, namely, that pulmonary resistance is a very sensitive indicator of the inhalation of respiratory tract irritants, and also to extend her observations on the influence of particulates in the potentiation of the effect of such irritants on pulmonary resistance.

In this connection, she had most interesting new observations, pointing out that with exposure for limited periods to an inert aerosol plus sulfur dioxide, the aerosol not only increased the total response in terms of pulmonary resistance but also delayed the return of the animal to normal. There was a prolongation of the net effect. This work is unquestionably highly significant in two senses: 1) In bringing to us a procedure whereby objective changes in pulmonary respiratory patterns can be measured for moderate levels of air pollutants; and, 2) in showing the potentiating effect of aerosols.

In the discussion of the potentiating effects, several mechanisms were discussed. Among them the point effect, and in this connection Dr. Goetz' observations were briefly mentioned. We hope that some time during the succeeding sessions Dr. Goetz may comment on this more fully. The possibility of chemical conversion of the sulfur dioxide to sulfuric acid as a factor of potentiation was discussed, but not resolved.

The next two papers came from Cincinnati, and represented separate reports on the studies being carried out by Dr. Shephard and Dr. Carey. These studies essentially involve an attempt to assess the time changes in a series of of clinical and physiological measures of a group of selected subjects who had either cardiac or respiratory difficulties or both, and to measure these against air pollution indices. They have had several years of experience with their procedures. They measure environment factors and they carry out physiological measurements. At the same time, they furnish the subjects with a diary form of record, to be completed by the subject. These various factors can be appraised and assessed against the environmental changes.

Dr. Carey pointed out that over the three years of experience with this study they have learned that the simpler the diary is, the more useful will the information be. They learned that the physiological tests that they were using could be improved; that some stood out as being highly efficient and others were less efficient. Timed tidal volume was one of the more efficient ones. Carbon monoxide uptake was also an efficient physiological measure.

This, then, was a report on improved techniques for conducting such a study. Dr. Carey also told us that they have worked to accumulate data, which needed to be machine analyzed. From this analysis it will be determined whether, in fact, changes could be detected in Cincinnati in the physiological or subjective responses of the patients to air pollutants.

Dr. Shephard, as part of the same study, reported on the more detailed techniques which they have attempted to apply to these subjects, under the general mode of approach of partitional respirometry. This is a procedure devised and described by Professor Hatch, and is a rather conprehensive group of physiological measures which can be used to determine several respiratory parameters. In the application of this procedure, Dr. Shephard described several limitations and means of improving and sharpening the technique, which he believes will make it more useful for its final and most rigorous application. He pointed out, however, that some data which may be critically important cannot be readily secured, *e.g.*, the cardiac output of the subject.

In the discussion of Dr. Shephard's paper, Dr. Meneely noted that the simplified compartmental system on which the technique was based may, in fact, be only an approximation, and some of the limitations inherent in this simplification may limit the sensitivity of its application.

This is a brief summary of the reports. Are there any questions? Dr. Goetz, would you like to comment on your concepts about the potentiation of irritant gases by particulates?

DR. GOETZ: The idea of the possibility of synergism between irritant gases and "neutral" particulate matter occurred to us and others quite early. In the literature, one can find indications of the concept about ten years ago.

In connection with smog, it has been our problem in Los Angeles to see whether there isn't a correlation between the occurrence of particulate forms and their formation, and physiological irritation. During the last two years we tried to see whether or not a biological reaction with such aerosols could be demonstrated by using some organism as an "irritation signal." Perhaps it is of interest to this group that so far, in exploratory stages, this has produced an affirmative answer.

We used E. coli as the test organism. We felt, that in order to demonstrate the effect of an aerosol, the bacterial bed had to be unprotected by buffering protective agents such as would occur if you bubbled the gas through a liquid broth culture. We, therefore, used membrane (millipore) filters. We put a counted number of organisms on the filter and exposed them to the impingement of the aerosols obtained from normal smog, from irradiated auto exhaust, or other sources. We thus demonstrated that there is a bactericidal effect under these conditions with the aerosol present in realistic concentrations. For instance, at twenty parts per billion of oxidant, which corresponds to a concentration that causes a medium degree of eye irritation, there was complete loss of viability of the E. coli organisms.

In a number of other ways, as well, the parallelism between eye irritation and the bacteriological effect signal became quite evident. For instance, if one filters the air through a membrane filter prior to impaction -- in other words, when one removes the particulate component of the smog -- the bacteria survive. The same occurs if you use non-irradiated automobile exhaust aerosols. Similarly, irradiated auto exhaust that was derived from the use of fuel types which are known not to lead to oxidant precursors, also give a negative response.

We hope that we may have found an inexpensive way, which is generally applicable and easily standardized, for measuring as substitute for human eye irritation. We believe, also, that in this way one can demonstrate when and to what extent a synergism between particulate matter and gaseous components occurs.

DR. NELSON: Thank you, Dr. Goetz.

The program chairman, Dr. Heimann, would like to say something at this time.

DR. HEIMANN: I would like to apologize to Mr. Hatch by saying it was my fault that his paper was not presented on time. I scheduled it improperly. If Mr. Hatch would like to take about five minutes to tell us something about his work on partitional respirometry, we would be very grateful.

MR. HATCH: I would like to do so.

Agents which are found in polluted community air apparently have no immediate acute effect on the healthy organism in the concentrations that are observed in such air.

Apparently, they may have a disastrous effect on the impaired individual. So it seemed to us of interest to reproduce, if possible, such a series of events in experimental animals.

The first question was: Could we artificially cause some kind and degree of respiratory impairment which would render the animal supersensitive to the agents at levels that would have meaning in relation to air pollution as it may occur? To do this, we used $NO_2$ as a damaging agent attempting to bring dogs to such a level of injury. When they are in this crippled state, we measure the degree of damage and the progression of the damage in terms of differential gas uptake, using ether, CO and acetylene.

The results thus far have brought out the startling conclusion that the respiratory system will take a tremendous amount of injury before it breaks down! We have exposed dogs to $NO_2$ for thirty minutes at levels of 50, 80, 120, 250, and 400 parts per million. As a result of thirty minutes' exposure to any one of these levels of $NO_2$ we have not had any deaths. That is, the dogs survived such exposures up to and including 400 parts per million for thirty minutes. They survived not only one exposure, but some of them survived several such exposures that were spaced some time apart.

In terms of change in the capacity to take up the test gases, (ether, CO, and acetylene), we found no evidence of disturbance in the animal at the previous exposure levels of 50 and 80 parts per million of $NO_2$. There is some evidence of a change at 120 p.p.m., greater evidence at 250 p.p.m., and quite remarkable loss of gas exchange capacity following exposure to 400 parts per million.

This is what we found in a typical experiment. At six hours following exposure to 270 p.p.m., there was a drop from 75 percent uptake of ether to about 50 percent. At the end of the day there was a rise; then there was a further drop and, finally, recovery again. At the end of a week, the dog had recovered from the depression in his ability to take up the test gas.

Starting out with a pre-exposure uptake of about 65 percent of carbon monoxide, it dropped to around 20 percent within six hours. The drop persisted for roughly two days and then there was recovery. At the end of a week the CO uptake was back to about the level of 65 percent with which it had started. Acetylene uptake dropped in about the same manner as the CO, and recovered similarly.

The respiratory volume of the animal, the pre-exposure level of which was about one liter per minute, rose in six hours to about three liters per minute, and was accompanied by a rather dramatic increase in breathing frequency. It then fell back to its original level in this manner. (Indicating.)

The drop in ether uptake can be largely accounted for by the increased breathing frequency. As a consequence of the increased frequency, with a more or less constant dead space, the percentage of the inhaled air that reached the respiratory portion of the lungs decreased, so that the drop in the ether uptake and its return upward generally followed the change in breathing frequency.

However, the changes in CO and acetylene uptake were out of proportion to that of ether. This means that there was real damage further down in the lungs which was not accounted for solely by the change in the efficiency with which the air was being taken into the lung.

If we multiply the percentage uptake for each of these gases by the minute volume, we get an expression of the gas transfer capacity of the system. This procedure would then reveal to what degree, through compensatory mechanisms, the animal was capable of offsetting the damage. When we did this we found that the ether uptake went up in such manner as this (indicating), and came down (indicating). That is, the rate of transfer of the gas into the animal was elevated in proportion to the increase in the rate at which the gas was being brought to the lung. This is as one would expect, unless there were some damage in that quarter. With respect to the carbon monoxide, there was practically no change, and similarly with regard to the acetylene.

The interpretation that I place on this is that, insofar as the respiratory process was operating to compensate for the damage which had been brought about as a result of the $NO_2$ exposure, the fact that there was no change in the actual rate of transfer in equivalent liters per minute of those gases means that the animal, despite the considerable damage to the process, was able to compensate for it quite successfully, so as to maintain the same rate of uptake.

In relation to the normal value of about 65 percent for CO uptake, the lowest figure that we have carried animals down to has been about nine percent. This means a very extensive disturbance of the gas exchange process; and, even these animals recovered from this experience.

In some very preliminary work with animals who have been reduced down to 20 percent CO uptake, we introduced a further insult with 100 p.p.m., $SO_2$. This resulted in a further depression of the respiratory process. As I recall, we exposed one animal to $SO_2$ at a time when his CO uptake was 23 percent, and that carried him further down to 14 percent uptake; but, dispite this further insult, the animal survived. So, we have not yet succeeded in bringing about any kind or degree of damage which was found to produce the critical state in past acute air pollution episodes.

We think that it will be more profitable to do progressive damage over a longer period of time and possibly in that way to produce a more permanent kind of damage.

DR. HEIMANN: I am sorry that there is no time for you to ask Mr. Hatch any questions, formally. I am sure that if you will talk with him later he will be glad to try to answer your questions.

The next panel was entitled, "Air Pollution And Eye Irritation." Mr. Krackow was chairman of that panel.

MR. KRACKOW: The panel of eye irritation and air pollution started with a few remarks by Dr. Leslie Chambers from Los Angeles. He gave us a progress report of the eye irritation studies done during the last 12 to 18 months in Los Angeles. Essentially he went into some of the procedures used to try to correlate the various components in smog with the incidence of eye irritation. He referred to some statistical methods developed by Dr. Merrifield, that would work if there were a sufficient amount of data. It broke down for the study of the years 1956 and 1957, because eye irritation in Los Angeles during those years was of a low order of frequency.

Another method mentioned, was that of Syrek. Here there was some degree of success in an attempt to correlate components in the atmosphere with the incidence of eye irritation. Up to a point there was success, in that oxidant levels could be correlated with eye irritation when the other components were held constant. He then went on to a discussion of Orcutt's method, which showed correlation between the hours of 8:00 a.m. to 4:30 p.m., but during the rest of the time the correlation was very poor.

Then Dr. Chambers made mention of the air components which he felt were in some way responsible for the eye effect experienced in Los Angeles. Mention was made that ether-soluble aerosols are necessary for eye irritation and that the aerosol factor is an important one. In this connection, he talked of Dr. Goetz' work. One of the items noted by Dr. Goetz was that when particulates were removed from the atmosphere, eye irritation was reduced or possibly disappeared. He also noted that at high temperatures the sub-micron particles seemed to release the eye irritant.

Dr. Chambers pointed up the importance of the olefinic hydrocarbons-unsaturated hydrocarbons-and $NO_2$; the fact that the $NO_2$ and olefins, upon solar irradiation combine to form a lacrimator. Then he mentioned that formic acid has been found in the atmosphere, and the belief that formaldehyde may be a factor in eye irritation.

Then, Dr. Mettier, representing a San Francisco group, presented a laboratory study in animals in which the eyes of rabbits had sections of their corneal epithelium stripped, and various exposures of those eyes made. In a sense this represented studies of physiology at the cellular level of the eye. Some eye biochemical studies, involving certain enzymes, were also studied. Preliminary studies were carried out exposing this eye preparation to ozone and to acrolien. The results that we saw did not demonstrate a very clear-cut picture.

The discussion of the papers brought up several interesting viewpoints. One viewpoint was that we need an objective approach to the problem of eye irritation. We had various shades of opinion as to how far to go in an objective type of study, and how far to go in a subjective type of study. I think that we left the question open.

DR. RENZETTI: I wonder if there was some misunderstanding about the effects of aerosol on the eye irritation. You said it removed eye irritation. As I recall Dr. Goetz' data, it only reduced the level of eye irritation.

MR. KRACKOW: That is correct.

DR. GOETZ: It is true that it was only a reduction; but, it was a substantial one.

DR. HEIMANN: Are there any more questions?

DR. MCKEE: I would like to inquire if there is any work in progress to determine whether or not it might be possible for chlorinated hydrocarbons to cause eye irritation. I am specifically thinking of areas about industrial plants, such as when chlorine plants and oil refineries are in close proximity to each other.

DR. STOKINGER: I would not think that there is any evidence that chlorinated hydrocarbons would be incriminated as an eye irritant. Chlorinated ketones, and things of that sort might do so; but, not chlorinated hydrocarbons.

DR. HEIMANN: Our next panel was on the subject of "Air Pollution And Cancer." Dr. John Goldsmith was chairman.

**DR. JOHN GOLDSMITH:** The panel on "Air Pollution And Cancer" was marked by considerable informality. Dr. Hueper was unable to be present to give his paper. Dr. Gilliam, one of our commentators, reviewed the epidemiology of lung cancer as it may be related to air pollution. I think that to best describe the work which Dr. Hueper has directed, I shall read the abstract of his paper. It is entitled "A Study Of The Relative Carcinogenic Potential Of Community Particulate Air Pollutants: Preliminary Report."

"The experimental studies conducted by the Environmental Cancer Section, NCI, in support of the Air Pollution Program, and with the cooperation of the Sanitary Engineering Center and of Dr. Paul Kotin, University of Southern California, have as their aim the demonstration of carcinogenic air pollutants, in the particulate phase, of eight metropolitan areas varying among themselves in their relative lung cancer morbidity and mortality rates and in the quantitative and qualitative chemical composition of the particulate phase of the air pollutants.

"Standard amounts of various fractions of air pollutants collected and chemically analyzed by the Sanitary Engineering Center are subcutaneously injected once a month into C-57 black mice for a maximal period of 24 months. Any carcinogenic responses which might be obtained with the different pollutants will be compared concerning their frequency, time of appearance and time at which they reach 1 cm. in diameter with the corresponding aspects observed in two series of mice subcutaneously injected with 3,4-benzpyrene. Both series consist of several sets given identical total and progressively increasing doses of the carcinogen. The mice of one series receive this dose by a single injection, while in the second series the total amount is administered in 12 fractionated doses.

"It is hoped that the results of this exploratory investigation on mice might, to some degree, reflect the qualitative and quantitative differences in the chemical composition of the particulate phases and the variations in lung cancer morbidity and mortality rates of the different metropolitan areas, thereby providing additional and significant factual evidence in support of the causal role of atmospheric pollutants in the causation of lung cancer and of their irregular epidemiologic pattern." This completes Dr. Hueper's abstract.

The presentation by Dr. Norton Nelson was, I think, a very stimulating one in which he called attention to the fact that most previous experimental work on lung cancer, with the exception of Dr. Vorwald's, had been using as an end point the production of skin cancer in animals or the enhanced appearance of lung adenoma in specific strains of mice. Dr. Nelson took as his goal the production of true bronchogenic carcinomas and he considered four possible methods of dosing the animals. He reported data for both mice and rats and, to a very limited extent, rabbits. The four methods were inhalation, tracheal injection, and two newer methods. Of the newer methods, the first consisted of the deposition of the suspected carcinogen on a thread and then the transfixion of that thread in the lung. The second was the intrabronchial implantation of a wire-mesh pellet which contained the potential carcinogen; the pellet was retained in the bronchus by a hook-like arrangement at one end. Both of these new methods required a surgical approach.

He used methylcholanthrene and dibenzanthracene. The first two methods, inhalation experiments and tracheal injection, did not yield any malignant tumors; but the second two methods did. The proportion of sarcoma and carcinoma differed between these two agents, methylcholanthrene causing a somewhat greater number of sarcomata and fewer carcinomata. One of the questions asked of Dr. Nelson was why this should be. We all agreed that we did not know.

The discussion of this paper led to the enunciation of two fairly important principles which it illustrated. One was that the agent which may be thought to produce cancer must be kept in contact for a long period of time with the cells with which it reacts. Secondly, that the production of cancer in this experiment appeared to require some tissue damage. The discussion then centered on the concept that the normal tracheobronchial tree has three barriers to the action of carcinogens on the sensitive cells, namely, the mucus layer, the cilia, and the palisading epithelium. The discussion of this point called to mind the work of Auerback on people who smoked cigarettes. He found hypertrophy of the basement cell layer and metaplasia of the columnar epithelium.

Dr. Gilliam was kind enough to discuss some of the epidemiologic aspects relating air pollution exposures to lung cancer. He pointed out the importance of the urban factor, by which is meant the fact that people who live in urbanized areas have substantially greater rates of lung cancer than people who live in rural areas. He listed three types of evidence linking air pollution of some sort to lung cancer, one of them being the effectiveness of so-called "private" air pollution that is occasioned by the smoking of cigarettes. The others were the occupational exposures which have been known to lead to lung cancer and the urban factor itself.

In discussing this paper Dr. Mancuso directed our attention to the fact that the urban-rural ratio was even greater for esophageal cancer than it was for lung cancer, and that the urban factor may be significant in other diseases as well. Dr. Mancuso emphasized the importance of obtaining basic epidemiologic data, such as the relative rates of lung cancer in husband-wife pairs. In another example, he noted the desirability of a study for long periods of workers whose industrial exposure consisted of exposure to a single, fairly-well classified chemical.

One of the points which is worthy of re-emphasis came out in the discussion of Dr. Nelson's paper. That is, it is very important to know what substance is reacting with the sensitive cell before drawing conclusions as to the ability to predict biologic reactions. I attempted to point out that some of the same reasoning applied to other experiments, in which substances found in air cannot be effective until they enter an aqueous phase; but, the substances which occur in the aqueous phase need not be the same as those which were originally put into the atmosphere.

CAPTAIN BABIONE: I think Dr. Brieger in his paper may have given us a clue to the relation between esophageal cancers and inhalation. It is no surprise to me to find esophageal cancers occurring from carcinogens that are inhaled, since we know that the tracheobronchial cilia pick up most of the particulate matter, carry it to the pharynx, and it is swallowed. This is known to occur for cigarette tar. In half an hour the cilia will carry a great part of the cigarette tar from the trachea into the pharynx.

DR. GOLDSMITH: I believe Dr. Levin also has shown some similar sort of relationship for gastric cancer, at least with respect to occupational exposures.

DR. HEIMANN: The next panel was on "Air Pollution And Allergy." Dr. Whittenberger, Harvard University School of Public Health, was the chairman for this panel.

DR. WHITTENBERGER: There were only two presentations on this part of the program. The first dealt with a type of natural air pollution, that of pollens in the atmosphere. Dr. Hewson spoke for a research team at the University of Michigan, a team which included internists, botanists, statisticians and allergists, as well as meteorologists. He described a technique that they developed, which permits the study of meteorologic influences on the dissemination over wide areas of ragweed pollen from a point source. The technique consists essentially of manipulation of environmental conditions, so that pollination can be induced in June, for example, at a time when there are not other natural sources of ragweed pollen in the atmosphere.

Dr. Hewson described the sampling grid and instrumentation and gave preliminary results of these meteorological studies. He described an apparently new hybrid variety of perennial ragweed and also indicated that there is some evidence that there is an eastward migration of perennial ragweed.

Dr. Hewson also described methods used in the study of prisoners in one of the state prisons in Michigan. In that study precise sampling is done of the pollens in the air and pulmonary function tests are done upon selected inmates. He also described exposure chambers for controlled human experiments with pollens. It is hoped to establish threshold limits of pollen concentration in patients with uncomplicated hay fever.

The second presentation had to do with immunochemical changes associated with the inhalation of respiratory tract irritants. Dr. Scheel, of the Occupational Health Field Headquarters, described his development of a new approach to the study of biologic reactions to chemical irritants. Among other things, he examined the effect of ozone on proteins, both in vitro and in the whole animal. Egg albumin, for example, was treated by heat and by exposure to ozone and the antibody responses to these natural and treated proteins were studied in the intact rabbit. The intact rabbit had no antibodies to these proteins and altered proteins, or such antibodies in insignificant amounts. But rabbits that had previously been exposed to ozone had a highly significant amount of such antibody which reacted with the previously ozone-treated egg albumin. Presumably, then, a similar antigen is formed in the body when ozone reacts with cellular protein. The implications of this type of response to chemical agents have not yet been worked out; but, the method offers possibilities of identifying the nature of previous chemical exposures and to help explain tolerance and hypersensitivity phenomena in respect to chemical agents.

In the discussion, Captain Babione illustrated some of these implications in a number of situations.

DR. HEIMANN: Are there any questions anyone would like to raise?

DR. HEWSON: I might say we have medical results, but they are rather anomalous. This is one reason I did not go into them. For example, we have found that hay fever symptoms in the morning increase some time before pollen concentrations. This is a result that we have verified, and is one that we obviously want to look into further. And that asthma symptoms follow pollen count much better than hay fever symptoms. We have quite a body of medical results, but, as I say, they are not subject to easy interpretation.

**DR. HEIMANN:** The next panel, the last one that we had, discussed "Community Health Studies Of Air Pollution." Dr. Mancuso acted as chairman for the panel.

**DR. MANCUSO:** I am going to differ from the others who made their presentations, because I feel that the detailed information is available to you in the form of the abstracts. Perhaps, instead, I might be able to give you an over-all picture of what happened and the patterns that developed during the discussions, and then give some additional thoughts.

The group of investigators, as represented in the seven panels, recognized the need to approach the problem simultaneously from the laboratory, the clinical and the community standpoints. Each is essential, but not a solution in itself.

The panel on Community Health Studies brought out some of the problems and methods for study, based on collecting frequency data for the sick and the well. In such studies of community health the effort as presented was to relate the sickness pattern within a community to levels of air pollution. This was illustrated by the characterization of the community by mapping the air pollution, as reported by Mr. Landau for the Los Angeles basin and Dr. Zeidberg for Nashville. These take advantage of knowledge of the distribution of air pollution.

The other studies presented attempts to establish a relationship between air pollution changes and exacerabations of certain illnesses. This was illustrated by Dr. Goldsmith on the relation to chronic bronchitis, by Dr. Schoettlin on patients with bronchial asthma, and by Mr. Manos on the disabled war veterans. From these studies certain problems of methodology become apparent. The first was the matter of accuracy of diagnosis of the specific disease conditions when the data are collected in various ways. The second group of problems involved especially in follow-up, were the changes that take place in the disease itself, the movement of the person from the area, the losses due to death, and others.

It was made clear throughout the discussions that, to understand the long-term clinical effects of exposure to air pollution, it is going to require repeated observations over long periods of time. This is also needed if we want to determine the later effects of acute toxic exposures. An illustration of the latter point was the follow-up study of Donora, as briefly reported by Dr. Thompson. Observations on cohort studies also appear to be desirable. Finally, an attempt was made by Mr. Manos at the development of an index of air pollution to be correlated with mortality rates, among other things.

The concepts involved in the presentations and the questions raised in the discussion re-emphasized the need for investigations which will study the effects of several variables, such as place of residence, occupation, smoking habits, socio-economic and other demographic characteristics, as well as dosage of the pollutant and time of exposure to it. All of these points were considered by Dr. Gilliam in his presentation of the principles of epidemiology as applied to atmospheric pollution.

It is our feeling that the role of community health studies is to (1) "pinpoint" problems that should be investigated in the laboratory and clinic and (2) to apply the findings of the laboratory and clinic to the control of disease conditions associated with atmospheric pollution. For example, consider the past epidemiological study of the disease, pellagra. Community studies produced indications that diet was associated with pellagra. Knowledge of the availability of only certain foods, the socio-economic differences and the age differences, all contributed to the hypothesis of a deficiency in diet as the cause. Laboratory experiments followed, and produced the disease, "black tongue," in dogs by means of diet. Later the specific deficiency for pellagra in man was identified and synthesized.

A second example that I may site is "retrolental fibroplasia," a disease that causes blindness in babies. The epidemiologist observed that there was an increasing incidence of early blindness in babies and, further, that the blindness was concentrated among premature babies. It was further observed that there was a marked difference in case occurrence between "teaching hospitals" and "non-teaching hospitals." Further consideration of the factors involved focused attention on the availability of incubators and this led to the theory of the harmful effect of high oxygen inhalation. Clinical trials and laboratory experiments followed and established the oxygen relationship and this led, finally, to a change in procedure in hospitals.

Our panel touched on only a few of the kinds of epidemiological studies which could be undertaken. While the methodological approach may be similar, the specific objectives of the studies may differ. Investigators in community health studies, although moving ahead within the readily apparent limitations, are also waiting for further hints from the clinician and the laboratory. It is hoped that this will come about in time for our meeting next year.

DR. HEIMANN: This closes our sessions on the medical studies. The meeting is adjourned.

## Arthur C. Stern, Chairman

This session convened at 9:00 a.m. in the auditorium of the Robert A. Taft Sanitary Engineering Center, Cincinnati, Ohio.

**MR. STERN**: In this final session we are going to minimize the words of the chairman of the session and maximize the time available to the six committee chairmen for their reports of the efforts of their committee during the past 1-1/2 days, and also to you for discussion. So without further ado we will get started with the final report of the Aerosol Committee, and I will ask the chairman, Dr. Chambers, to come forward and present his report.

## Aerosol Committee Report

**DR. CHAMBERS**: I am going to follow this report pretty closely because I assume that, having been handed out to you so recently, you haven't had a chance to read it and I think it forms the only suitable basis for discussion of the deliberations of the committee.

As anticipated, it has proved difficult to consider the solid and liquid phases of the atmosphere apart from the gas phase and instrumentation required for measurement and analysis. In consequence, the proceedings of the Aerosol Committee may have overlapped those of other groups and the following summary report in all probability infringes, at some points, the assigned interests of some of the other committees.

The status of knowledge of atmospheric aerosols is such that there is need for substantial research and development in almost all phases. A major shift of interest has occurred recently as the result of apparent demonstrations that aerosols, in addition to their nuisance values as primary entities, also participate in and are a part of reaction systems in polluted community atmospheres. They appear to be related closely to processes resulting in oxidations, in the formation of irritants and potential toxicants, and their intervention may influence the mechanisms and rates of photochemical processes. In addition, the visibility reduction already identified with primary aerosols appears to be strongly fortified by the formation and growth of secondary aerosols, particularly under the influence of solar radiation.

The expansion of research activity relative to aerosols has resulted directly from the design and use of instruments and methods specifically designed to assess the more or less transient properties of particles in dynamic equilibrium with a reactive gaseous environment. Future advances in knowledge of the properties of this class of pollutants will be largely dependent on the successful development of mensuration and analytical techniques of sufficient resolving power to enable the determination of spatial properties and events in a size range difficult to examine by optical means and having a limited existence in time.

It is clearly recognized that the exigencies of various local air pollution control problems require the prompt accumulation of certain measurements and other data applicable to identification of sources, patterns of aerial distribution, and design and evaluation of aerosol control techniques and equipment. Because of the more apparent than real dichotomy of interests among those participating, the following areas of recommended research interest are divided into two general categories. One comprises studies specifically directed toward analysis of the physiocochemical system involved and including the aerosols. The second includes project areas from which needed control data can be derived with reasonable speed. No effort has been made to establish priority of effort respecting either of these groups.

The first category is: Recommended research areas aimed at understanding the system to be controlled. There are five areas.

1) The study of the formation, growth, and fate of aerosols.

Evidence was presented indicating that there is a close relationship between the formative process for particulates of certain types and the development of irritative and other nuisance properties in irradiated atmospheric systems. It is further agreed that knowledge is needed of the persistence of both primary and secondary aerosols and of the mechanisms by which they are cleared from the atmosphere.

2) Investigations of the interaction between particles and their gaseous environments.

It was agreed that intensive studies should be directed toward the determination of the dynamic equilibrium dependence of such systems on: (a) the nature of the gas, (b) the chemical species of the particle, (c) the size of the particle, (d) the temperature of the system, (e) the luminous flux, and (f) the partial pressure and particle density of the system.

The conduct of work in this area will require the development or modification of instrumental techniques having a high order of precision and capable of considerable resolution with respect to both linear dimensions and time. The concept of dynamic equilibrium implies that attention be paid to transient intermediate chemical products and states of adsorption, as well as to the build-up of terminal products. Obviously, initial efforts toward definition of the properties of aerosol gas systems should be patterned as nearly as practicable on the basis of what is already known about the content of atmospheres in communities troubled by air pollution.

3) Investigations designed to characterize air-borne particles with respect to composition, surface energy state, electrical charge, and other experimentally determinable parameters.

In a sense, the type of information to be produced in these studies will be basic to the study of equilibrium phenomena proposed in the preceding project area.

4) Studies of the sensitization of photochemical oxidations and other reactions at the interface between particle and gas.

Recent work has indicated that certain metallic oxides and other solid substances may intervene strongly in the types of photochemical processes which have already been described as existing over several communities. Estimates of the quantitative contribution of surface phenomena of this type to the air pollution problem requires investigation.

5) Investigations of the relationship of aerosols and their process of formation and growth to the production of eye irritants, plant damage, and other evidences of pollution.

Strong evidence was presented before the committee indicating that a relationship exists between the aerosol phase of a polluted atmosphere and the degree to which that atmosphere is capable of causing eye irritation after irradiation by sunlight.

Now for the second category: Recommended research areas for immediate application in existing control programs:

1) The collection and collation of available data on the size, shape, physical properties, and chemical nature of particles from identified sources of pollution.

It is believed that publication of a compendium of methods, identifying characteristics, and photographs would be of material assistance in local operations aimed at control of specific classes of source.

2) Expansion of surveys for the establishment of patterns of variation in the distribution of aerosols in relation to discrete and to disperse sources.

This type of investigation is already in process in a few fortunate localities but has not yet developed to such a degree that is possible to establish generalizations of wide applicability. These studies necessarily involve measurements of meteorological factors as well as the contaminants.

3) Development of specific measurement and analytical techniques and instrumentation.

While this field of interest was specifically assigned to the Instrumentation Committee, the Aerosol Committee wishes to emphasize the extreme importance attached to the need for adequate and relatively inexpensive devices easily applied to field assignments.

4) Studies of atmospheric transparency as related to aerosol content in the community atmosphere.

Probably the largest single need for adequate correlation of visibility with other atmospheric measurements is a useable inexpensive instrument for measuring light transmission and light scattering. Again it is assumed that requirements in this connection merely reinforce the need recognized by the Instrumentation Committee.

5) Research designed to contribute to source control of aerosols.

In particular, it is felt that additional analyses of distribution patterns from individual sources are needed; that a considerable amount of improvement can be attained with respect to the suppression and control of aerosols at the source, and that the employment of specific tracers in the analysis of distribution from primary sources should be more fully explored. Presumably, recommendations covering these needs will be made by the Committee on Engineering.

It may be apparent that no account has been taken in this report of the problems surrounding biological aerosols or radioactive particulate matter in the atmosphere. While these two areas were discussed by the Committee, it was generally agreed that under existing conditions of distribution of interest it was not appropriate for the Committee to do more than recognize the existence of occasional problems involving these two classes of pollutants.

This does not intend to imply that biological entities or radioactive tracers should not be employed in the process of exploring research wise any of the problems required. We're talking here about a primary interest in these entities as pollutants.

Now I'd like to add one other word, which is more a personal opinion than a consensus of the committee. I think it is apparent that we have not attempted to assign any dollar value nor any estimate of the man power required to solve these. In this connection, I think it is always well to emphasize that there is more need for excellent quality in type of research required for the solution of some of these very complex systems, particularly those involving the dynamic equilibrium with which we deal, than there is for the pumping into the program of huge amounts of money. Money will be necessary, but brains and skills of a very high order are going to be more necessary. The atmospheric situation in most areas is such that any workable understanding of the complex situations that exists is going to require the interest of agencies, laboratories, and persons who have a wide variety of highly developed skills in the specific disciplines necessary. Thank You.

MR. STERN: The report is now open for discussion.

(No discussion)

MR. STERN: You apparently feel that the committee itself has taken all the dissenting opinions, worked them over, and has included them in the report, so that it has now become acceptable to all of you. We will therefore proceed to the report of the Agricultural Committee, to be presented by Dr. F. E. Gartrell.

## Agricultural Committee Report

**DR. GARTRELL:** I would like to take this opportunity to express my appreciation to the members of the committee for their hard work. By the time we broke up last night it was impossible to get their attention long enough to do that. I would also like to express the thanks of the committee to Dr. Brandt and Dr. Emge who refused to be considered as members of the committee but I assure you that, for all practical purposes, they were and we are thankful to them for their help. Arthur Stern has mentioned gratefulness to Don Keagy and from now on out, as far as I'm concerned, he is "the needle." If it hadn't been for the needling that Don gave me -- and I'm sure that some of the others of you shared that privilege -- this seminar could not have gone off as smoothly as it has. It certainly has been a pleasure to work with Don and others of the staff, to the extent I have been privileged to, in connection with this seminar.

I've found acting as chairman for this small and spirited group to be quite an experience and it had some of the elements of a rocket trip to outer space. The very beginning of our discussion consisted of a "blast off" in which rather violent issue was taken with some of the statements the chairman had made at the opening meeting of this seminar. It was not until the second stage had fired off that I realized the launching was likely to be successful, and that there was a possibility that we might eventually get in orbit and travel the course that we had so carefully plotted for ourselves. When we started orbiting there was a slight feeling of relief because for a while when we felt we were going completely into outer space and would wind up on the moon. I'm sure we would have found it quite difficult to report back to you today if that had occurred. But, we got in orbit finally and went round and round. Then we were faced with the problem of reentry. I can assure you that we have solved that problem successfully and we found -- as so many investigators in this field have found -- the problem is one of heat dissipation. The heat from some of the discussions we had, caused this to be quite a problem. But be that as it may, one part of this trip turned out to be less of a chore than we had thought it might be. That was the matter of decoding the "beeps" and the "beefs" that had been so faithfully recorded by Dr. McNulty who had acted as our secretary. And so we were able to meet this "Simon Legree" deadline -- that Arthur Stern always sets for meetings of this kind -- and I assure you it is a pleasure for me to present this report to you.

Air pollution research as it affects agriculture has had, and is receiving, considerable attention in many problem areas. However, the work in this field has not been sufficiently organized on a national basis. Special problems have received special emphasis, so that much of the work has been of a fortuitous nature. Last year's report of this committee provided a good summary of some of the major problems needing attention, and gave particular priority to fluorine effects as needing research in the immediate future. It is recognized that the greatest sparsity of information exists in the field of fundamental research; however, numerous problems still need to be solved in the applied field. It is recognized that some advances in these areas have been made during the past year.

Some modifications of that report have been suggested by this year's committee. These include: (1) added stress on the determination and diagnosis of injuries that may result from exposure to relatively low level concentrations of pollutants over long periods, (2) effects of gas mixtures, (3) improved damage survey techniques, and (4) the orientation of fundamental research programs to the effects of field encountered concentrations of major pollutants on vital plant processes.

Now that some of the more obvious effects of single air contaminant compounds to certain crop plants and animals can be readily recognized, new emphasis will likely be placed on the detection of the less obvious, but still important, effects, and on injuries to economic crop plants, trees, and animals that have received scant attention in the past.

Research on the effects of air pollution upon the national agricultural economy is usually stimulated by local pressure groups concerned with a specific grievance. Although this admittedly allows the description of the problem, the motivation generally does not provide a sound basis for an integrated interdisciplinary research effort. Investigations are, at times, initiated because funds are made available to an investigator already involved in a related field of study. Other programs are begun either because the effects cannot be specifically ascribed to known air contaminants or the effect of a newly recognized air contaminant is not known.

It is generally conceded that research established for the purpose of determining the effects of specific contaminants upon livestock and vegetation must be conducted under controlled or described conditions which recognize experienced toxicant concentrations, genetic composition, nutritional status, physiologic function, and external environmental factors. Programs of this kind not only satisfy the local needs for information but aid greatly in acceleration of research activity at a national level.

Exchange of ideas among air pollution research administrators is not nearly as important as it is among research workers. Common avenues of exchange include national science conclaves, specific society activities, symposia, and personal contact. The establishment of periodicals dedicated to the multidisciplinary field of research in air pollution, together with an appropriate abstracting service, will do much to foster exchange of ideas.

The committee recommends that the U. S. Public Health Service continue to maintain liaison with private, industrial and public research organizations. The committee further recommends that the pioneering research laboratories of the U. S. Department of Agriculture undertake basic research on air pollution affecting plants and animals. The committee urges that in research studies emphasis be placed on realistic levels of concentrations and related environmental factors experienced under field conditions.

The need is recognized for establishment of a means for active encouragement of current publication of results of air pollution studies, for periodic critical reviews of technical publications, and for provision of authoritative information in this field. Possibilities for meeting this need should be explored.

We urge that meetings of this kind be continued and that regional symposia be held to provide for the type of information interchange needed to lead, in the near future, to a more coordinated research program on the effects of air contamination on all phases of agriculture and forestry. The air pollution program may well consider inviting administrators to attend the next meeting for discussion of research programs and exchange of ideas. Private industry, states, colleges, research institutes, and the Federal Government should all continue to feel a responsibility for parts in such a coordinated program.

MR. STERN: This report is open for discussion and the floor is now yours.

DR. LODGE: I think that possibly some of the group here is not aware that there is a new International Journal of Air Pollution. I notice that the need for an interdisciplinary journal was referred to here. This is being published by Pergamon in England and is specifically oriented toward publishing research papers rather than reviews and collections of data. I think it may provide the outlet that we need for the publication of interdisciplinary papers in the field.

**FROM THE FLOOR:** Mr. Stern, Mr. Pier is apparently too modest to give a commercial for the Air Pollution Control Association. Its journal and its abstracting service are very fine publications.

**MR. PIER:** Thank You.

**MR. STERN:** Apparently we have reached the same stage of successful presentation in connection with this report as with the previous one: the digestive processes of the committee have been satisfactory to the group. We will take advantage of the gain in time to proceed with the next Chemical Committee report by Dr. Philip W. West.

## Chemical Committee Report

**DR. WEST:** Gentlemen, the Chemical Committee had very interesting sessions, the results of which have been summarized. I think I will let you read this report, (Appendix A), and you can see the scope of our deliberations.

I would like to mention that the Chemical Committee was limited to discussions of analytical problems. Not that atmospheric chemistry was not of interest nor that atmospheric chemistry was not considered important but by the time that we had spent the time available on the analytical problems, we found that there was not enough time remaining to devote to the chemistry of the atmosphere. Further, since some of the people whom we would like most to have with us for such discussions were attending other sessions, we thought it would be unwise to proceed without them.

Our discussions began with the consideration of sampling techniques. Here we quickly realized that, while progress is being made, sampling still remains one of the greatest problems in air pollution work. The emphasis on organic pollutants requires, of course, new techniques -- all the way through to the sampling of organic pollutants. This was of special interest to us yesterday.

We talked about adsorption techniques and freeze-out techniques. We ultimately concluded that they both were valid and both would have places of application. However, we thought it would be wise for more critical studies to be made comparing the two methods. We felt that possibly the restriction placed on sampling, by problems of air pollution surveys, might somewhat obviate some of the previous thoughts concerning the relative usefulness of these two methods. Certainly both of these methods will find use and someone undoubtedly will look into the matter of the best places to use each of the two methods.

Grab samples were discussed and here again we find that there is much to be done. We were in general agreement that we wanted to have more of a trend toward specific or selective adsorbers; particularly adsorbers that would not only selectively extract pollutants from the air being purged, but would also fix the pollutant in such a condition that further change in composition, or subsequent reaction with other trapped materials, would be minimized if not completely eliminated.

Gas-liquid chromatography, of course, was one of the techniques discussed rather completely. It was felt that this too was one of the truly useful techniques that has been made available to us in recent times. There were words of caution from some members who pointed out that just because retention time has been given, such values do not necessarily mean that identification can be obtained. However, it was also agreed that, for many atmospheres where it can be anticipated that certain pollutants might be present, it would be quite reasonable to assume that a given retention time on a calibrated column would be highly indicative. And further, that by trapping an effluent gas, recycling it on another column, and again obtaining the anticipated retention time, good evidence would be obtained that the materials indicated were actually present.

It was certainly unanimous that gas-liquid chromatography would become a very useful tool in separating pollutants for subsequent study by other techniques. Incidentally - - I might add here -- one of the comments made was to the effect that we had no good methods for detecting or identifying the peaks. This may be true in part but even mass spectrometry and infrared techniques are not perfect. We still need more analytical methods than those now available to us so that we can apply them to the various problems that faced us in air pollution work.

Naturally infrared spectrometry was discussed. The long-path infrared techniques certainly have given us a tremendous amount of information and in many cases, as we see it now, these techniques are the only ones that can be applied to the study of a dynamic system where other methods would fail. The cost of the equipment is great and we had some argument about how much skill was required in operating the instruments. Certainly, we all admire the puzzle-work that has been done in this field to date and possibly in the future we will see more routine work being done as the techniques become simplified. In the meantime, I think we must give tribute to those people who have developed the method and have applied it so effectively.

The ring-oven technique was discussed and since this is a new technique to most people, I think it proved to be of general interest to the Chemical Committee. We have included a reference in the report so that those who wish can read a description of this method. I might add that nothing has been done in the air pollution field in the application of this technique as yet except for some preliminary studies that we ourselves have made. There is every indication that this could be a very useful method in studying air pollution problems.

Mass spectrometry certainly is of importance and we look forward to, and hope for, more work in its use. As a research tool, this is going to be, as it has been in the past, a most valuable tool.

Polarography and anodic stripping voltammetry. Polarography has been used to some extent. The sensitivity is not as great as we would like but for certain studies, particularly in the identification and estimation of organic compounds, it has rather unique advantages. In passing, we might mention that voltammetry which has a sensitivity in the order of 10-10 or possibly 10-14 grams of material, certainly holds promise in the estimation of inorganic materials.

Microwave spectrometry was discussed.

Dust identification has already been mentioned in the Aerosol Report and it seems that we are concurring closely here on some of the valuable methods that can be applied in the identification of dust.

Biological methods have not been used as fully as they might be and we look to the future here, feeling that more biological techniques will be developed.

Miscellaneous techniques were skipped over. We realized that there were many tools available to us and that undoubtedly some of these would develop into valuable assets in the work of the air pollution analyst.

Special problems were recognized. Studies of nitroolefins, and other organic nitro compounds; peroxides; organohalogen compounds; boron compounds; fluorides; the organic sulfides and mercaptans; carcinogenic compounds; all of these require a great deal of additional work.

Nothing was said about the work in progress in various laboratories in the opening remarks that I gave on Wednesday but we might mention that we have many active centers for research for the development of analytical methods for air pollution, and also for the study of atmospheric chemistry. I might just mention these briefly to give you some sort of orientation: At Pittsburgh Coke and Chemical, activated charcoal absorbers are being studied. At the University of Michigan, carbon monoxide and its effects on accident rates are under study. At the University of Illinois, oxides of nitrogen. At the

Franklin Institute, the long-path infrared spectroscope and its use in the study of various problems such as the L. A. smog, etc., is under investigation. At McCrone Associates, studies on dust identification will continue. At Kansas State, structure studies on the oxides of nitrogen are now in the initial stages of development. At Wayne University, work has dealt primarily with phenolic compounds - their collection and estimation. At the Environmental Research Laboratory, pulp mill effluents, gas-liquid chromatography, dustfall, electrostatic precipitators, and cascade collectors are under investigation. The Bureau of Standards has a wide program of research -- we know that they are applying mass spectrometry and other tools. At Southwest Research - the analysis of particulates from auto exhausts. At Stanford Research Institute - goodness knows how many things they're working on - collection efficiencies for particulate materials, smogs of various types, etc., are being studied. At Oxford, going abroad, some interesting work has been done on ozone. In Germany, the work is on industrial hygiene detectors - Drager tubes, etc. - - and phase contrast microscopy. In Italy, Dr. Vittori's laboratories are working on micro-spot tests -- that is a precipitation test. A wide variety of things are going on here at the Sanitary Engineering Center. In our own laboratories, we are working on gas-liquid chromatography and $N_2O_5$. We are doing some work on the ring oven and are working on the development of field kits.

All in all, the group had some very interesting sessions and in concluding my remarks I wish to express appreciation to Don Keagy, Mr. Stern, Dr. Lodge and others here at the Center who have helped us so much. I think that these sessions are extremely stimulating and whether we have reports or not is beside the point. This get-together with people as outstanding as this group is, I think, stimulating enough for most of us.

Thank You.

DR. GARTRELL: Would you tell me what a ring oven is?

**DR. WEST:** The ring oven was developed by Herbert Weisz in Vienna, Austria and it was described for the first time about four years ago, possibly five now. I saw it demonstrated about three years ago, which was shortly after it had been developed. Using a single drop of material, Dr. Weisz ran through the old hydrogen sulfide qual scheme, and in about twenty minutes, I think, he identified 14 different metals. The method is extremely elegant. It is just one of those things someone should have thought of years ago. It is a very effective means of attaining separation and of concentrating materials. In air pollution work there are certainly many possible applications - - particularly in the identification and estimation of dust, and constituents in dust and aerosol materials that might be collected on filters. In essence, it is a heated ring, about 20 millimeters in diameter, with an open chamber underneath. A filter paper is placed on top of this. A little spot of dust, or precipitate, or whatever it is, is centered very accurately in this ring. Solvents are then added by means of a capillary pipette. These solvents flow over the precipitate, or dust, and extract whatever is soluble. The extract diffuses out through the pores of the filter paper to the heated periphery, the ring, where they are deposited. In this way, everything that was in the center that is soluble is transferred out to the ring. The transfer is beautifully quantitative and very efficient. About four to eight washings are all that are required for complete separation. The resulting concentrated ring of salt, or whatever you've got, can then be analyzed. You can cut that ring into segments and run spot tests on each area. Thus you can identify the various metals in there. Or, you can stamp out the remaining precipitate, or dust, put that on a fresh paper, and use a different solvent. Or, you can go through a whole sequence of separations and have a very effective means of quickly obtaining separations. The concentrated material in the ring can be estimated quantitatively with fair accuracy. I think we will find quite a bit of use for it in air pollution work. It is not going to solve very many of our major problems but it will be a useful tool.

**DR. LODGE:** I'd like to put in parenthetically - you say quantitative work can be done with suitable accuracy. I don't believe this quite underlines the accuracy obtainable. This is the first time I had seen this quantative technique at all and yet under Dr. Weisz's guidance I did the estimation of a total of about one and one-half micrograms of iron with a precision of approximately seven percent, which is slightly poorer than average. Usually, it can be done within five percent, which I think will beat polarography.

**FROM THE FLOOR:** Did the Chemical Committee consider standard samples?

**DR. WEST:** I imagine implied there is standardization of methods. Consideration was really not given to this because it was felt at this time nothing much has been done. It was discussed, however. It has been hoped by Dr. Lodge and some of the other people interested in these methods, that some sort of a cooperative study could be set up whereby certain laboratories -- say universities or research centers in various parts of the country -- might look over available methods and possibly make recommendations concerning procedures for certain types of problems. This turned out to be disappointing in that financial support was required, and no financial support seemed forthcoming. I think we all feel the need for this. I might also mention that there was discussion of the terminology and the units that are used in air pollution work. Most of us were quite unhappy with the present method of reporting results. We would like to see more uniform units applied. But again, this is being considered, I believe, in other committees and we did not devote any time to it.

**MR. STERN:** Mr. Kramer can give us some information about the reference services the Center offers through its training group which is now very effective in the field of water analysis.

**MR. KRAMER:** I believe we have, as Arthur says, a program that is directed toward the very points under discussion. It is titled the Analytical Reference Service. This activity has a broad objective in terms of evaluation of old and the introduction of new laboratory methods. We have begun by making up synthetic samples in water at concentrations of interest in this field.

Our Type One sample covers perhaps the most elementary types of determinations that would be performed on waters throughout the country. Our second type sample contained eight heavy metals. On these samples we merely give the qualitative make-up to our members, the participating laboratories, and they in turn perform the study using the methods that they routinely employ. They return replicate values to us and criticize the methods employed, especially their weaknesses and deficiencies. This enables us to record observations and opinions in addition to the accuracy and precision attained. We are preparing a report covering our third type sample which involves the study of a new analytical method. Based upon extensive study and consultation we thought that a new method, appearing in the literature might be superior to any of those currently in practice for a particular determination. We announced a sample that would permit the evaluation of this method with various types of interferences present. A detailed step by step procedure was supplied. We furnished the dye as well. In this study we obtained the analytical values for the sample on both this new method and on the method they were using routinely.

We have been considering for some time the broadening of this program to include air. I think this step would be most helpful since there isn't the degree of standardization in air analysis that has occurred with water. The availability of such a sample will be announced in the very near future. We now have copies of reports on some of the samples that we have studied, should any of you care to examine them. I should say, too, that Dr. Chambers was very instrumental in helping us initiate this program.

I should also mention that we have another type sample in preparation: a water sample for radiological evaluations. Here the cooperating laboratories will go through the complete process of preparation, evaporation, and counting. By an evaluation of results from a large number of laboratories, we will be able to estimate the precision and accuracy that we can expect in this type of determination today.

FROM THE FLOOR: Would you outline the techniques used in this gas-liquid chromatography? I know some of us, in physics and meteorology are not familiar with what this technique is.

DR. WEST: Gas-liquid chromatography itself, or specifically some of the techniques applied to air pollution?

FROM THE FLOOR: Just what is chromatography? The word chrome means color to me. It also is a material used on cars.

DR. WEST: Yes, it is a misnomer. Chromatography originally dealt with colored substances being isolated from leaves, carrots, and tomatoes, and the name was carried on long after the color aspect became less important. In gas-liquid chromatography we have an extremely powerful tool for analyzing gases. In general the technique involves introducing a gas or volatile liquid into a column of very small diameter that is packed with some solid material -- it might be just ground up fire brick. This solid material serves to hold, in a fixed position, a non-volatile liquid. The gas sample is swept through this column by means of a carrier gas such as helium or hydrogen. As the carrier sweeps through the tube the sample is carried down along the column and is gradually separated into its components, depending upon the relative solubilities and volatilities of these components, in the immobile liquid. Finally the sample components are eluted from the far end of the column and can be detected by a thermal conductivity cell or some other suitable measurement. Originally, A. V. P. Martin, who invented the technique, just arbitrarily caught fractions and carried out titrations to see what was coming out.

The material that is analyzed is separated into fractions and by noting the time it takes for a given component to go through the column, one obtains some sort of an identification. In some cases you can go from one column to another, say three columns, and you'll get different times of retention. If they check in all three columns with anticipated retention times, you're fairly certain that identity has been established. This is a very useful and very sensitive means of separating and also of estimating the quantity and identity of the material present.

DR. ALTSHULLER: If anyone from any of the other committees or the other disciplines is interested, we do have a gas chromatography in operation up on the fourth floor, which we would be glad to show you along with various optical instruments.

DR. LODGE: We also have laboratories working on various other kinds of chromatography; including paper, partition, adsorption, and several others.

DR. BREIDENBACH: It was mentioned that there is a lack of uniformity in the use of units in expressing concentrations, etc. There was a very interesting paper presented at the Mid-Atlantic States Meeting of theAir Pollution Control Association on the "Recommended Units of Expression for Air Pollution."

DR. WEST: Yes. That was mentioned yesterday and in fact, Dr. Lodge brought a copy of that in for me to see.

DR. RENZETTI: I'd like to suggest that this preoccupation with the analytical phase be directed toward some real chemical problems. I have about five or six examples that might be put on the record.

In case you didn't realize it, a definitive relationship between ozone and oxidant has not been established in the Los Angeles smog. I believe it may await the development of analytical methods but this is still a fruitful bit of chemistry yet to do. One which is in a worse state is the nitrogen chemistry in Los Angeles smog. I'd like to also invite your attention to the fact that the eye irritant has not been identified in this smog, nor has the plant damaging component been found. Getting along to more practical questions which I believe will have to come out of chemical research is the question of the ability to reduce NO at the source. And finally, in this branch of chemical research, investigations of the combustibility of very low concentrations of organic materials are needed. Being perhaps naive in the other fields of air pollution, I'd like to ask could someone tell me if the sulfur chemistry --- not in the laboratory system but in the actual complex polluted atmosphere --- is understood, and if so could he explain it to me?

DR. WEST: I think probably some of the members of the Chemical Committee might want to answer your question. Jim has the answer maybe?

DR. LODGE: I have answers. I don't have the answer. In regard to the list of things we need analytical methods for, I think if you will examine the Chemical Report these are listed - more or less specifically - as being things that we recommend looking into. In the second place, as far as the sulfur chemistry is concerned, there are a couple of pieces of the sulfur cycle that I feel pretty good about now. There are several others that were mentioned in passing during deliberations of the committee and it was pointed out that we know nothing about these portions, or so close to nothing that we might as well say we know nothing about it. I think, Dr. Renzetti, there is work on all of the phases of the problem you have listed here going on some place. In most cases it is safe to say it is going on in several places, but there are no answers yet.

MR. GRUBER: I would like to emphasize one point that Dr. Chambers made -- the need for more simplified techniques. In my official capacity, I face the problem day in and day out of monitoring complex streams of air either in flood conditions or stagnant pools over the 75 square miles of the city of Cincinnati. Therefore, this question of simplified techniques is certainly important to me. Another point I think is very important is the field of dust identification. I'd like to ask concerning the extent of work being done along this line.

DR. WEST: Well, Walter McCrone is working on that and we are doing some work in that field. There are many laboratories working on dust identification. There are studies right here at the Center on organic particulate matter. It's just a matter of a lot of time and work required -- it is not a simple problem. We mentioned the ring oven just because it does present a possible neat, simple approach to solving some of the more sticky separations and difficulties associated with dust identifications.

MR. GRUBER: We have a problem in the taking of a sample of dust or the lifting of a sample in order to study it. Many cases start with a complainant showing an inspector the dust, on the furniture, or the porch, or on his merchandise. The problem is lifting the sample so it can be studied and identified. I suggest work along this line.

DR. WEST: Les, do you want to comment on this?

DR. CHAMBERS: I think Charlie Gruber and I have discussed this numbers of times. I recognize his problem because we have much the same sort of a problem, perhaps in a little different form in Los Angeles. There are about as many ways of collecting samples of particulates from specific kinds of sources as there are specific kinds of sources. In other words, you have to continue to adapt methods to the nature of the material and to the circumstance of collection. Perhaps they could be simplified but in most cases I believe methods which are satisfactory, for control purposes at least, are available. In some cases they are more complicated, possibly, than we would like to have them for routine operations.

We have to balance the desire for economy against the necessity of getting the job done hurriedly, so that not in all cases are efforts made to economize and to reduce the operation to the simplest possible terms and methods. In sampling for some types of materials from some types of sources we may be up against a consideration that if we really want to know something about them you've got to spend the effort and money necessary to get the information.

**MR. STERN:** Thank you very much. I should now like to call on the chairman of the Engineering Committee, Mr. Charles E. Lapple.

## Engineering Committee Report

**MR. LAPPLE:** Gentlemen: The deliberations of our committee have been concerned with the various aspects of the air pollution problem as it involves engineering. This includes the evaluation of the need for and the extent of control measures and the economic application of the indicated control both at the source and in the field. The committee feels that the rate of progress in the engineering aspects of air pollution has been comparably inadequate in the light of the economic importance of the problem. This reflects primarily two things: first, the relatively low expenditure in research relative to the cost of air pollution; and second, of these research funds that are being spent, the relatively large amount that goes into engineering application rather than actual research.

It is therefore the considered opinion of the Committee that future research activities lean more heavily to the basic side than has been the case. With this in mind, our recommendations have been expressed in rather broad categories rather than giving specific, maybe important, but isolated items.

Our committee also wishes to reiterate the conclusion drawn at the last Air Pollution Research Planning Seminar that control at the source by process design or modification is a most desirable approach. We recognize, however, that in many cases effective control by this means may not be generally economically feasible. Because of the wide variety of problems encountered and because of the many intangibles that have to be considered in decisions involving process design and modification, our committee also feels that this area is not a fruitful area for research. We do not intend to preclude, by this, the desirability of doing research in this area in specific instances nor do we wish to reflect on the desirability of emphasizing this aspect in design considerations.

Before going to our specific recommendations I might give just a few points on how our deliberations went, how they were organized, and what the basis of our conclusions was. We finally wound up in splitting into two groups because of the rather distinct demarcation between the two phases which had to be considered by the large committee, and because of the very large field of activity that we had to cover. One group delt entirely with particulates; the other group with odors, vapors, and gases. Finally following the deliberations and the conclusions of both committees, there was a joint meeting of the two groups and then a meeting of representatives from each group to combine the results of both sub-groups. In general, we tried to put things into general, broad categories not giving any priority to dollar figures because we did not -- we tried at first -- see how we could even come close to arriving at such figures; even less in getting agreement thereon.

We did set up our recommendations on the basis of what we thought was important to do. In that sense, our recommendations have a priority and we feel that the items mentioned here are the important ones to be accomplished. There were a number of other items discussed but left out of our recommendations, largely because we felt they were less important than those mentioned. In trying to combine the work of these two groups and bring it into a common form, I might add, that any resemblance between the end results and the deliberations are purely coincidental. However, at the moment, at least until I hear a minority report, I think I am safe in saying that the conclusions do represent the consensus of the entire committee.

We have split our recommendations into three general categories: (1) those concerning the characteristics and quantity of atmospheric contaminants; (2) evaluation techniques; and (3) control measures.

Under characteristics and quantity of atmospheric contaminants, our committee believes that there is an urgent need for a compendium of the nature and amounts of specific atmospheric contaminants. Such a compendium, in conjunction with other data on the effects of specific contaminants, would provide, first, a basis for assessing the air pollution potential of a specific city or area; secondly a basis for assessing the relative need for control measures for specific contaminants in that area; and, thirdly, a basis for formulating or revising specific air pollution control regulations for that area. While compendia of this type have been obtained in specific instances, it is the intent to enlarge and generalize such information. The first step in assembling such a compendium would provide a classification by operation or process, or by industry. Further analysis and correlation might provide useful information on the bases of broader classifications such as geographical area, industrial concentration, etc. To enhance the potential applicability of these data, attempts should also be made to correlate the data on such bases as quantity of contaminant per capita, per dollar sales, per employee, etc. Such correlations, in essence, represent an attempt to arrive at techniques analogous to those used in market surveys.

There is also an urgent need for fundamental bases for extending information on quantity of emission of a contaminant, or its precursor, to actual field manifestations. The first step in such a relationship requires the development of basic information on the deposition and retention of particulates, gases, and vapors on surfaces of all kinds, such as walls, ground, vegetation, etc. The subsequent effects of such retained deposits are in the domain of the other committees concerned with specific areas of effect, such as agricultural damage.

The results of such an investigation would also be applicable in the area of remedial equipment performance, in which area some work on deposition has already been carried out. There has been substantially no work along the lines of particle retentivity, for example.

It has been customary to characterize particulates by size. The committee wishes to emphasize that particle size is rarely measured directly. Some other characteristic of the particle is measured which is then interpreted in terms of an effective size by means of some theoretical or empirical relationship. In considering the behavior of a particle in some apparatus or process, it is therefore, essential that the method of measurement used to obtain the effective particle size involve a measure of the same characteristic of the particle which determines its behavior in the process or equipment under consideration. For example, in defining the performance of inertial separators, it is the particle inertia which is of prime importance. The effective size of such a particle should then be based on a measurement which involves the inertia of the particle, such as settling velocity. In other devices, such as cloth collectors, other characteristics, not yet clearly defined, are of prime importance. It is desirable, therefore, to specify or, for cases which are yet unknown, to develop the basis to be used for particle size specification in a variety of operations. The question of characterizing a particle in terms of effective particle size is merely a matter of semantics. It is essential, however, that the inherent characteristic described by this effective size be clearly kept in mind in relation to the operation under consideration.

It has also been widespread practice to measure particle size in terms of size of the discrete particles. In an air stream the particles are not necessarily present as discrete particles but are flocculated to a greater or lesser extent, depending on the previous history. The behavior of the particles will be determined by the characteristics, not of the individual particles, but of the flocs as a whole. It is essential, therefore, that the measurement aimed at characterizing such particles in gas suspension measure the characteristic of the flocs as they exist in the gas stream and not the characteristic property of the discrete particles. Failure to consider this distinction has often introduced major fallacies in arriving at conclusions.

Thus the "effective" particle size, as we will use every time we refer to particle size in the rest of this discussion, refers to a size based on a measurement of the characteristic property of the particles as they exist in suspension, the specific characteristic property being determined by the particular application under consideration.

The principles of particle behavior have been determined largely for atmospheric temperature and pressure conditions. While, in some cases, in fact in most cases, theoretical bases exist for applying the principles to high temperatures, other factors may enter or become controlling at elevated temperatures. Therefore, with the current importance of high temperature operation, it is imperative that experimental and theoretical investigations be undertaken to establish -- which may mean simply confirming -- principles of particle behavior at elevated temperatures.

Now we come to evaluation techniques. Our committee feels that progress in the application of engineering to the control of particulates is most seriously limited by the current inadequacy of lack of two basic tools. The committee as a whole felt it is the weakest link in the entire engineering aspect. The two tools that we lack are: First, a means for reproducibly generating both solid and liquid test aerosols, of relatively homogeneous size, and relatively complete dispersion in a range of size from, say, 0.1 to 10 microns, and with a variety of materials and shapes.

While several techniques are currently available for this purpose, they all involve serious limitations either in quantity of aerosol produced, flexibility, or in control. In other words, we don't wish to say that techniques are not available or have not been used. We simply say that the techniques are not flexible enough or do not lend themselves to engineering scale evaluations. The second tool we lack is a means for measuring "effective" particle size, as we have defined previously, for a variety of pertinent characteristic properties, and applicable for the measurements of size of particles as they exist in suspension, not as we take them in the form of a powder and then measure the size of discrete particles.

The committee strongly recommends that development in these two areas receive high priority on both short term and long term bases. In the evaluation of particulate control equipment, the use of so-called "standard" test dusts has received great prominence. This has been a necessity because of a lack of better means of evaluation. Because of the inherent limitations and the relative futility of past evaluations by this means, the committee feels that, except for special areas of application, the emphasis on development of such dusts be minimized in favor of a greater emphasis on generation of homogeneous aerosols, as previously mentioned. The Committee recognizes that, in the interim, "standard" test dusts will still find a role in current equipment evaluation.

One serious drawback to the further progress of control of gaseous contaminants is the limitation imposed by subjective measurements. It is, therefore, suggested that consideration be given to further development and refinement of subjective measurements of gaseous contaminants such as eye irritants and odors. It is believed desirable to investigate the feasibility of physical and chemical methods related to subjective methods with a view to supplementing these methods. The development of these techniques may logically fall within the scope of disciplines other than engineering.

Now, on to control measures. It was felt that sufficient importance has not been attached to the air pollution problem in the process development and plant design phase. We, therefore, recommend that an effort be made to make engineers sufficiently aware of the air pollution problem so that it will receive adequate consideration in design. The best method for this that I've known in the past is to have them face a lawsuit. The next design will receive a little more consideration.

While there has been considerable evaluation of the performance of remedial equipment in specific applications, there is an extensive need for information which is both more definitive of comparative performance characteristics and more generally applicable to a variety of problems. The committee suggests, therefore, that the evaluation of remedial equipment performance be conducted at a more basic level than has been the case, utilizing where available and applicable, techniques of the types we have discussed previously. It is not uncommon, and may be desirable, to carry along technique developments and equipment evaluation simultaneously. The above mentioned evaluation should be aimed at developing sound selection and design criteria for remedial equipment installation.

The committee recognizes that work is in progress in development of remedial measures for removal of contaminants from combustion and pyrometallurgical process exhausts. This includes such items as the internal combustion engines, steam-generating facilities, metallurgical furnaces, incinerators, etc. The committee believes, however, that accelerated research is indicated, aimed not only toward the development of adequate equipment but also to a more thorough economic comparison of alternative equipment. Such research must consider not only the mechanical operability at elevated temperatures but any unique factors introduced by the elevated temperatures on performance characteristics.

Finally, the committee also recommends that evaluations be made to determine the feasibility of fuel modifications for the removal of specific components which contribute to the formation of noxious gaseous constituents.

I would also like to take this opportunity to thank my committee members for the cooperation received and especially to those individuals who stayed up the last several nights to put this report together. Thank you.

MR. STERN: Do we have any questions? Any comments?

DR. RENZETTI: Do you see any limitation to the use of the light-scattering technique in the measurement of particles as they exist in the atmosphere?

MR. LAPPLE: Actually, I feel the long-range potential of the light-scattering technique is excellent. In other words, it is the kind of thing we are looking for. What is basically missing at the moment is the fact that there is not much confirmation of the light-scattering technique. At the moment it rests largely on theoretical relationships. There has been little work done toward confirming these relationships, especially as they are applied to irregular particles and other-than-transparent particles, that is, colored or opaque.

DR. RENZETTI: You mean the index of refraction of the dust is not known.

MR. LAPPLE: Among other things, yes. We would like nothing better than to get a light-scattering technique that we can rely on over a wide range of concentrations with any shape, color, or opacity of particles. That would be the answer to our maiden's dream.

DR. RENZETTI: How about the particle spectrometer, which is a settling - velocity - type analyzer with laminar flow. It presumably captures particles as they exist in the air stream because the removal is very gentle.

MR. LAPPLE: That technique has been used. There have been three groups, that I know of, that have used the same technique, apparently independently, at about the same time. Hemeon has used it, Goetz has used it, and we have used it. It still has limitations. It is the only technique that we actually know of at the moment that has a good engineering applicability to measure what I've termed "effective" size. It still has limitations from the analytical stand-point of obtaining a cheap, fast, measurement.

**MR. STERN:** I think we are going to have to defer further questions until later --- and call Dr. Renzetti to report for the Instrumentation Committee.

## Instrumentation Committee Report

**DR. RENZETTI:** I feel so overlapped by now that you may not hear anything new. I do have the advantage that you have not heard from the Meteorology Group and they can take care of me accordingly.

I wish first to thank the efforts of our committee and Mr. John Nader of the Center for making it possible to reduce this extensive conversation to a few well chosen words. I'm not going to read this report, (Appendix B). I'd like to just emphasize a few points and perhaps the philosophy that came out of our discussion.

I hope I've covered in writing, in detail, what actually is the state of the art and what is the need in the various fields, with one exception, namely the meteorology field, which I understand will be covered by that group.

To put it very simply we think the atmospheric analysis picture, gas-phase wise, is in urgent need of a field instrument which is based on quite different principles than have been used to a large extent so far. I'm going to try to think back. Why the reason? Why are we stuck with this rather bad situation of $4,000 recorders. If you look back you will see that most of them came out of some intensive laboratory programs to try to understand what is going on in the laboratory situation. There was no time to really engineer this equipment to field use. It was quickly brought out into the field to assess the air pollution problem as it was demanded by the community. So there wasn't sufficient time to really sit back and say, "Now this is what we want to measure. Let's be practical about this and lock for a principle that is susceptible to a portable cheap instrument."

The committee thinks there are two areas wherein someone should take the time to sit back and work on them real hard. They offer potentialities.

The first is that of combining some of the techniques developed by the particulate work over the last twenty-five years in passing a gas volume through a filter paper. This kind of thing has been done many times in all varieties of ways and in a lot of equipment already developed. A lot of the components of such a system are on hand and one should spend his time looking for reagents which can be put into the filter paper, filter medium, or the matrix, or whatever you want to call it, which will give the reaction with a particular gas that you want to monitor, and developing, of course, the suitable standards which are necessary.

The second area is the use of the physical properties of the gases for their own identification and concentration measurement rather than through the chemical reactions which are so predominant in the present instrumentation. However, here one has a somewhat longer way to go. For example, in radiation spectrometry we have such a principle but we are still a long way from an inexpensive instrument. We think the direction there is probably filter photometers which may have to have folded paths in order to get sufficient sensitivity. One has the gain here of a lot of work going on in the field of the infrared, especially for the military.

Solid-state physics is developing components that will make it practical for the air pollution people to have, we believe, filter photometers in a wide variety of applications by simply substituting one cell for another for the particular gas. It has been demonstrated quite clearly in Los Angeles, for example, that the CO analyzer is just an ideal instrument from a community point of view. It is easy to operate in the field, and lacks maintenance difficulties and all the associated problems with the wet chemistry that we have. Well, this is the main point we wish to get across in the field of gas-phase atmospheric analysis: Start thinking about these recording colorimeters and spend some time on either of these two other areas because we think they will be a big pay off in reaching our goal.

In the aerosol-phase of atmospheric analyses there are really three types of instruments that can be used. I think here we need the caution that Charlie Lapple gave us about what it is we want to measure about the physical characteristics. The biggest gap in the measurement of the number, density, and size distribution by the automatic means as provided us by electronic scattering, is the lack of index of refraction data on a wide variety of particulate matter in the atmosphere. This is circumvented somewhat by the particle spectrometer, but this has not at the moment reached the ideal stage of a field instrument. In determining the chemical nature of the dust particulate, the consensus of the committee was that, other than what can be done by placing the reagents in the filter on which one impinges the particulate, the only other hope is that you conduct your sampling program at the most effective level of economy and simplicity. Bring the problem back to the laboratory rather than dwell too much on the subject of trying to do chemical analysis in the field.

The third subject was meteorology and I will defer to the Meteorology Committee except to point out that we were unanimous in the need for visibility instrumentation. Our committee felt that what was needed now was a good evaluation program in the field correlating the visual index of visibility with the five types of instruments mentioned on page 3 of our report. These cover pretty well the principles that are likely to be usable in the field-type instrument. One need look, at the moment, at the results of this before proceeding in any other direction.

The subject of data processing of large amounts of atmospheric analyses received some discussion. It was pointed out that the state of the art is quite high in the field of not only computors and data processors but also, on the shelf, means of converting present instruments to eliminate the strip chart recorders, which are so common, and go directly to tape on punch card.

The next general area the committee discussed was: source analyses, gas phase. Again the general subject of spectrometers was prominent in that the most effective ones that we have today are like those for carbon monoxide, carbon dioxide and hydrocarbons, nitric oxide, $SO_2$, and $NO_2$ Spectrometers. Since one doesn't, in general, need a tremendous number of these instruments, these will probably satisfy the requirements for some time to come. This approach is to be looked to for new gases. There are specific needs for two types of instruments which are mentioned in the text.

In the aerosol phase, Charlie Lapple has already covered the needs here as we saw them. One additional one was the matter of plume evaluation. It seemed to us that the only way we could come to grips with this problem was to have some means of counting the particles if we are going to have an objective number index to characterize the plumes. The problemsassociated with all the other methods are subjective. They always will be subject to controversy and difficulties. Since the plume is a matter of visibility phenomena, it is a matter of counting the particles and relating those to the opacity that would be created by such a number density. However, we realize that there may be some complexity in this problem. Sometimes the physics and chemistry of the atmosphere are such that you may start out with quite a harmless emission from the plume point of view, but something happens either chemically or physically to bring the size range to where it is a community problem. This looks pretty difficult because you're faced with getting some characterization of the particles below 0.3 micron diameter. It was suggested by one member of the committee that perhaps the polorization of the light involved in the scattering might be sensitive to this size range.

Then one might eventually develop an instrument based on this principle. This is very much in the basic research stage.

Laboratory research-gas phase, the third general area, was pretty well circumscribed by the Chemical Group. They apparently went into everything we discussed in citing the advantages of pushing gas chromatography, (and) infrared and mass spectrometry. The contributions made by our committee to this is that there are some other things that one might look at --- to help elucidate this chemistry. One of them being long-path ultraviolet spectrometry which has not been applied yet to elucidating this chemistry. In other words, instrumentation-wise we look for infrared gas chromatography primarily as an aid and as a back-up to the program of mass spectrometry.

Finally, in studying the aerosol and the particulate matter in the laboratory, as against the engineering scale which Charlie mentioned, the situation is actually pretty good. Three major efforts have gone on and have come out with these techniques of light-scattering and centrifuging for studying the particulates in as near the state as it exists in the actual suspension as is possible. The outstanding problem there, in our committee's opinion, was to identify and characterize the adsorbed layer on a particulate which may be an important factor in characterizing the total aerosol. This is going to be a pretty difficult problem.

In the field of organic materials, again, we're going to rely on our folks on infrared spectrometry. This technique is being pushed by the petroleum industry in the study of catalytisis and one should look in that area for the break-through that can come in identifying these materials.

We are faced with the same situation in the source analyses when we have to study particles below 0.2 microns. We don't really have anything satisfactory. One definitely needs an extension of the present technology in light-scattering and centrifuging in order to make any hay in that area.

MR. STERN: We are open for questions or discussion on this report.

MR. LAPPLE: Would it be out of order at this moment to say a little more about light-scattering?

MR. STERN: No.

MR. LAPPLE: There is one point that I failed to make in discussing the engineering applicability of optical systems for size measurement and I feel this is rather important. That is to again emphasize the fact that, in engineering, we are not interested in the particle size. What we need in engineering are numbers which measure some characteristic property of the particle, usually a physical property though not necessarily so. We should note that the optical methods give us an effective optical size. Even this effective optical size has different meanings depending on the optical methods involved. That doesn't mean that optical methods cannot be used. What it does mean, though, is that the optical method, since it measures an effective optical size, requires one further step. That is a calibration between the optical characteristics for our material and the specific characteristic that we need for the engineering. The difficulty there lies in the fact that this characteristic property is different for different applications. In other words, depending upon the application, we need a different calibration for different characteristic property relationships to the optical properties.

DR. GOETZ: This has often entered into the discussion of that very question. Is it sound to assume that the optical properties characterize an aerosol particle, rather than its kinetic (Stokes) qualities? The latter determine the "fate" of the particle in the respiratory channels as well as in the atmosphere; i.e., its chances for coagulation and final disappearance. In other words, the optical properties seem to me a characterization of an aerosol which is not too informative from a public health point of view.

**MR. LAPPLE:** No, I think that is essentially correct. Any differences lie primarily in what application or what phase are we concerned with. From the visibility standpoint it would be directly associated with the optical properties. From the standpoint of vegetation damage, we're not sure. One thing is obviously the inertial property or the settling velocity -- inertial because of deposition by wind. In some cases, possibly, diffusional properties, they come a little closer to the optical ones. In the case of design of bag filters, for example, we have to know the combination of the bulking and permeability properties of the particles as they come together. We could just run a whole series of these properties -- theoretically an infinite number - which depend entirely upon what aspect of the problem we are concerned with.

**DR. GOETZ:** Is not the retention of aerosols in the submicron range on any screen-type filter determined by its Stokes' properties?

**MR. LAPPLE:** Let me rephrase the question. Essentially, you're asking: "What are the performance characteristics of filters as far as the particle properties are concerned?" Again there is a difference, depending on the operating conditions. If we take filters operating at very low velocity, we probably have diffusion and physical interception as the controlling mechanism. Now when we consider filters which operate, like domestic furnace filters, at high velocities, it is probably predominantly the inertial characteristic that is important.

We also have other factors. We have reason to believe that solid particles do not behave like liquid particles. All filtration work has been done, or I should say almost all of it has been done, on liquid aerosols. When they hit they may spread but they stick and theory assumes - or the present theory assumes - that, when a particle touches a surface it adheres to it. Theory holds quite well with liquid particles.

With solid particles we, and others, have found--and again the investigations are not exhaustive--that retention may be a major factor. When particles hit a solid surface, even small particles, the order of one micron, may fail to adhere. In other word, they may hit and bounce off again. This may not be just a ten percent factor, it may be a ten-fold factor. Actually very little work has been done on this aspect. The problem of retentivity is important in agriculture. Consider deposition of fluorides on vegetation, for example. We may have very small particles which deposit at such a slow rate they are probably not important. With larger particle sizes, which we feel are on the order of 3 microns, the deposition rate is roughly the same as that for a corresponding concentration of vapors. Then, as the particle gets larger, it theoretically should deposit more readily. But there must come a point where blow-off becomes important. Even though these larger particles may deposit more readily, they are also blown off more readily. So there must be an optimum size, or a minimal size, whichever way you wish to look at it, which gives the greatest agricultural deposition.

MR. FISHER: I was going to remark that there do exist some data on the applicability of optical and light scattering measurements to the study of particle behavior. Going back quite a few years to the work on efficient filtration of small size liquid aerosols, optical scattering measurements furnished some very useful information in developing some of the more efficient filters that we are all using now. More recently, we and others have been accumulating some additional data on some of these uses. For instance, we have used optical measurements for the study of the settling out of aerosol systems. We have found that the settling of aerosol clouds can be followed quite reasonably by the use of light scattering measurements to get relative numbers and size distributions of suspended particles. Sedimentation measurements done this way show definite correlations with measurements made by other methods.

With respect to the difficulty of interpreting optical size measurements, we usually have one of two situations: There are some systems in which light scattering size measurements seem to fail entirely. This is primarily due to the fact that we still lack a sufficiently sophisticated mathematical analysis of light scattering by polydisperse systems. There are other situations where approximate comparisons can be made between light scattering size measurements and data obtained by other methods. In these cases, it is often found that comparisons are quite difficult due to the severe limitations in the accuracy of other methods of particle size measurement. This creates situations in which there is no real basis for critical comparison of light scattering data with data from other methods. We have found some different uses for light scattering measurements. One such application, for instance, involved determining the charge distribution on suspended particles in preparation for electrostatic precipitation. Another application involved the correlation of particle concentrations with atmospheric visibility studies. In this latter case, the particle count by an optical method is, of course, directly applicable and such data have been widely used in this particular study to distinguish the particle scattering from the effects of other materials on visibility.

DR. LODGE: Isn't the situation here rather like the fellow who said, "I know it's crooked but it's the only game in town." So far the only technique that we have for particle sizing which can be completely automated is light-scattering. Therefore we strain to use it whether or not it actually measures the property of the aerosol system that we would like to measure. If we had a completely automatic technique for measuring inertial size, or Stokes size as Dr. Goetz says, in which we could just punch a button and the data would come out, we certainly would use that in many cases in which we now use light-scattering.

DR. CHAMBERS: In connection with Mr. Lapple's presentation, it seems to me that what was implied was that we've got a situation in which, when searching for a practical application of knowledge in its present state to engineering problems, we are looking for one simple solution to a multitude of problems. It seems reasonable that we are not going to arrive at a single solution to all of the problems that are involved. There's one thing that has bothered us a bit, or some of us in Los Angeles at any rate, in connection with the approach to control methods, or the assessment of approaches to control methods. We usually are requested by the engineers to provide a method which will measure some property of the emission. We usually then turn the tables and ask them what degree of accuracy and precision is required in the practical situation. And thus far the answer has been most unsatisfactory. I think there may be a tendency to try to push decimal points out to extremes without recognition of the fact that in a practical situation some of these theoretical complexities actually do not apply.

**MR. STERN:** Dr. Renzetti, did your committee consider the possibility of the development of instruments with less inherent accuracy to meet situations that need less inherent accuracy?

**DR. RENZETTI:** No.

**DR. ALTSHULLER:** Dr. Renzetti, I was interested in your need for the development of a ultraviolet cell. Is this just a general conclusion of the committee, or were there some particular chemical species that were discussed which emphasized the current need for the development of such a cell?

**DR. RENZETTI:** Well, I think it came up with reference to the Los Angeles situation, where some of the compounds, or the intermediates, might have more absorption in the ultraviolet than they do in infrared. We haven't seen any more in the last year or so of intermediate compounds in the infrared, so in a way, one should take an exploratory look at the ultraviolet.

**DR. CHAMBERS:** I might add that we have in operation now a folded path 25 meter ultraviolet cell.

**MR. LAPPLE:** I might add a few words in connection with the remarks made by Dr. Chambers.

We would like to get a method of particle size analysis that is universal; but we cannot expect it. In fact, I feel that it is inherently not in the cards. He mentioned this matter of engineering specifications and again I agree with him. I think too many times specifications are set entirely outside the realm of practicability. The engineer that sets them is not familiar enough with the limitations of the art to recognize this. I have often gotten into cases of equipment selection where arguments lasted for hours, because for one piece of equipment the vendor guaranteed 88 percent removal and another vendor guaranteed 90 percent. That to me is ridiculous. Other differences in the equipment are far greater than the difference between 88 percent and 90 percent guarantee. Dr. Lodge mentioned that optical methods are the only fast solution we have. Again I fully agree with that. I do wish to add that, from the standpoint of engineering, this matter of particle size analysis should be very carefully considered because there are a good many cases where an analysis by light-scattering, or by any other method, can yield worse information than no analysis at all. In other words, it is more misleading than it is informative. It is a source of more mistakes in practices than possibly any other single item.

MR. WHITBY: I'd like to make a comment relative to the engineering significance of air cleaner specifications. We have been studying, or trying to determine, what the minimum significant difference in the amount of penetration through an air cleaner might be from an engineering point of view. We came up with the general conclusion that a two-to-one difference in penetration is about the minimum significant difference. If this is translated back into particle size and efficiency specifications it turns out to be several orders of magnitude cruder than the majority of the people, who are experienced in the field, require.

MR. GRUBER: I would like to say that I hope this discussion of the optical methods and whatnot in measuring dust particles does not overshadow the first recommendation of the committee again which is this matter of simplified instruments and techniques. There is nothing particularly glamorous about an instrument which you squeeze and read a result immediately, but I'm telling you it can be mighty, mighty important in this work.

MR. STERN: We will now proceed to the final committee report. Dr. Malone now has twenty minutes to give the Meteorology Report.

## Meteorology Committee Report

**DR. MALONE:** So much has been said and so well said by my colleagues who chaired the other committees, that I find it rather difficult to follow in their footsteps and convey to this audience the enthusiasm and interest with which our particular group attacked the meteorological aspects of this overall problem. Perhaps I'll be excused for being brief this morning. After the late hours the last two nights I can't read anyway, so I will not read this report (Appendix C). I would like, in the time that Mr. Stern has very fairly set aside for me, to summarize some of the things that are touched upon our committee in report and draw your attention to a few of the considerations of our group.

The last 2-1/2 days have been extremely stimulating. I might say it has been an exciting climax to a rather spirited correspondence which has taken place among the members of our committee over the last two months. It's fashionable in research planning congresses to characterize areas, and we have done this. We've divided the meteorological contribution into three kinds.

The first is basic research. This is fundamental, of course, and actually gets down into the problem of anisotropic turbulence in the atmosphere. We deplore the fact that more work is not being done here. We are encouraged to believe that there is going to be increasing emphasis on basic meteorological research and we hope this aspect gets some attention because it is fundamental in the problem of air pollution.

The second is a sort of applied research which tends to mix up enough basic knowledge and awareness of the practical problem to give information directly applicable to the community air pollution problem.

The third category is the kind, which is listed here (in the report) as category 1. This is direct participation by meteorologists in specific community air pollution studies as a sort of professional consultant. I invite your attention to the several different services which the meteorologist is in a position to provide. I think we should not discount the knowledge that we do have. It's far from complete, but there are six specific things that the meteorologist knows and can do. You can read them so I won't bother.

Now, let's restrict our attention to the second category of meteorological research aimed at providing information directly applicable to the problem of community air pollution. In our discussions prior to coming here we tried to pick out from the whole litany of topics which might fall into this category, the one or two which we felt were fundamental and which we thought we should concentrate on while we were here.

The one finally settled upon was the dispersive power of the atmosphere. We asked ourselves this question, "Where do we stand with respect to this question of the dispersing power of the atmosphere?". I don't believe it is necessary for me to go into the reason for its application in the community air pollution problem. This is fundamental to control of air pollution. Here we said, "Do we need more theoretical work? Do we need more empirical work, observations and field studies? What are the prospects of using model techniques to advance this knowledge of dispersive power?" I was surprised at the unanimity of the replies that came in. It was felt that the theoretical work had preceeded about as far as it could go at the present time until this very basic study of anistropic turbulences was carried on further. It was felt that while model studies have great application - I invite your attention to a little discussion here endorsing more work on model studies - that the greatest application, the greatest opportunities for adding to our information about the dispersive power of the atmosphere, would be from actual observational studies. I think it was quite significant that there seemed to be in the minds of people scattered all the way from the east coast to the west coast a very definite feeling that we have reached the stage where it was time to put some of the things that we know together. And particularly to do this on the scale of the community air pollution problem. There has been quite a bit of work on somewhat smaller scale. The results have been encouraging enough to suggest that the same general method of study should be applied to the dimension that runs out to, say, fifty miles--to give you a feel for the size of the problem. But as soon as you do that, of course, it is necessary to make the vertical dimension commensurate with the horizontal dimension, so that the thing really grows up to a three-dimensional scaling problem.

Now, we think certain things should be done but the question came up, "Well, maybe we have these data--maybe information is available." We think there is quite a bit of information available and that this could be fully analyzed. Especially we feel very strongly about the matter touched upon on page 2 (of the report) and I invite your attention to the three middle paragraphs. I would summarize them by saying that our committee feels that it is completely inexcusable that observational information collected during studies involving security considerations have not been released. We made a recommendation last year that this should be done. Nothing has happened. Worse, we don't know why it hasn't happened and we think this is a deplorable situation. We are encouraged by the fact that information on "bow-and-arrow weapons", developed during World War II, are now being released. Maybe we could get some of this information which--it is the general feeling--would help solve some of these problems.

But even this information is not really going to answer the problem at hand. What is required is a full-scale integrated effort to establish suitable relationships between the dispersive capacity and meteorological parameters that serve as direct indicators of turbulent mixing, and to do this on a scale of the community air pollution problem. We have tried to lay down some of the specifications for the kind of experiment or integrated effort that we propose should be given serious consideration at this time. We talked on page 3 (of the report) about the scale; we talked a little about the site; we talked a little about the source; we talked a little bit about the measurements. Basically there are two aspects to the measurement. One is the three-dimensional distribution of a tracer effluent discharged from a continuous point source of known characteristics at various elevations. I know many of you are wondering, "Why are they worrying about a point source? That isn't the community air pollution problem." But going back to Dr. Gartrell's analogy of the rocket this morning. It is foolish to start talking about the second or third stage when you don't really understand the mechanism by which the first stage gets off. We believe that you've got to bring together the physics and the empiricism. This can be attacked by starting with the point source. As a matter of fact, it is not a matter of great moment to extend this to the multiple or area source and the kind of a program we've envisioning here is really aimed at being a little more realistic about the kind of sources that are actually involved in an air pollution problem.

The second aspect is concerned with the meteorological variables, and they are listed there if you would like to read them.

We have some idea about how long this kind of a program would take. We're actually conscious of the need, in fact of the necessity, of using the most sophisticated techniques for data processing. We believe that these are at hand. We, in our field of meteorology, are used to handling a tremendous quantity of data. We think nothing of putting ten million pieces of data on 704 tape and running through all kinds of computations. We don't believe the automation aspects have been developed to the degree that is available. They just haven't closed the gap here between what is available and what is being done in this community air pollution problem.

Now, not only are we concerned about the diffusion problems but some of our committee members feel very strongly that the deposition aspects, the fallout, impaction, wash out, rain out, snow out, have to be considered and could be considered in such a program. In talking about the type of field measurement which we feel would advance our understanding of this basic problem of dispersive power of the atmoshpere, we immediately get into some of the disciplines that have already been summarized here--initially the one of instrumentation and secondly, the one of tracer techniques.

We had a very fine discussion with some of Dr. Renzetti's people. We have listed a few of the areas in which we feel there is a need for a new or different kind of instrumentation. These have already been discussed to some extent. I would say that one area of importance that hasn't been discussed this morning involves measurements in the range of from 100 to 5000 feet from the ground. We have instruments for measuring all the way up to 100,000 feet but we don't do very well in the 100 to 5000 feet range. Furthermore, we don't believe that there is any thing in principle preventing this. We don't know exactly how to do it but everyone is agreed that our friends in the instrument division are so ingenious and so resourceful that they can solve this problem for us.

We are also optimistic about tracer techniques. I must confess to a little bit of confusion as an aftermath of the discussion this morning on tracer techniques. We were talking about tracer techniques being used now by meteorologists. I wonder if you people are being overly modest, or if you are seeking refinement, or precision, which is greater than we need? We had the impression during our discussions that there are some problems here, but in essence the ability to use the kind of tracer techniques that we would want are almost at hand, and at a cost which is not unreasonable in view of the economic significance of this whole problem. We've listed some of the specifications we'd like, on page 5 (of the report). I would invite the comment of Dr. West's group on that type of thing. We, as did others, stress simplicity, durability, low cost, and the general type of measurement which is not restricted to a specific problem. There is, on page 6 (of the report), a discussion of the role of models in air pollution.

Now, what have we accomplished? Mr. Stern, we are deeply grateful to you and your people for this opportunity to come together and have these discussions. There were some ideas changed in the last 2-1/2 days. Some positions were altered as a result of getting together, of hammering out arguments, and of discussing some evidence, and batting things back and forth. Our committee would like to acknowledge the work of Don Keagy and of Ray Wanta in putting this together and making this such a pleasant session.

I think that the significant thing from our standpoint is this: That from many different independent sources, in the area of the meteorological aspects of air pollution, has come the recognition -- and I've got 16 pages of specific recommendations from different people of how this should be done -- of the need for pulling together now in a single, integrated effort some of the work that has been done in fragmented form. Some of these small projects have been very fruitful, but there is a limit to how far you can fragmentize research. I get the feeling this morning, that we're going off rather far along our own specialties. Some of you people are talking about things I don't understand, yet we're supposedly in the same field. I wonder if there isn't a tendency to get so refined, so specialized, so engrossed in a particular study, that somewhere along the way we've still got to pull things together. And, while this is desirable, we feel very much that in order to solve the problem which is now ready for attack we're going to have to consolidate at least some of the effort and some of the things that have been discussed this morning. In other words, we're right at the stage now where there is so much knowledge that it's time to think about pulling some of it together without sacrificing continued specialized research efforts.

Thank you.

**MR. STERN:** I think we'll go into a combined general discussion and discussion of this presentation. So the floor is wide open to shoot questions or to comment on Dr. Malone's presentation or any other.

**DR. MCKEE:** I would like to comment on one possible field of study that may have been neglected more than it should have been. Speaking as one who is not a meteorologist, it seems to me that it would be important to study the fine structure and variations within a given parcel of air. There is some evidence that a parcel of air, even as small as a few cubic meters, is not homogeneous within itself. I can think of two bits of evidence for this. One is the results with the Kruger Ozone Analyzer, which Dr. Chambers mentioned a year ago, in which very rapid and wide swings in ozone concentration were measured in short time intervals. The other is the observation that two thermocouples temperature indicators a few feet apart in the air will measure different temperatures by several degrees. The only requirement is that they be rapid-response temperature-sensing devices of some kind.

It seems to me that if there is this variability within a small parcel of air, this phenomenon would be important in studying diffusion from a point source and this then would be applicable to the study of community air pollution. One example of how this might be studied would be the development of instruments to measure other things besides ozone with a short response time. Most of the present continuous recorders have a response time of 30 seconds on up, and if we can measure $SO_2$, or $NO_2$, or other pollutants in the air with a response time of a second, or a half of a second, or some such time, a study of such data along with related meteorological data might be very revealing.

**DR. MALONE:** You're quite right of course. This is fundamental to the whole problem of pollution. It is not being by-passed. There is work going on, on this specific thing, but we would put this in the basic research category. It does seem possible to integrate over some of these small eddies and arrive at answers by some kind of a short-cut method which would provide immediate information and we addressed ourselves to that particular approach.

DR. CHAMBERS: Well, again, getting back to a practical point of view, Herb (McKee), what do you believe to be the present indication of a requirement for such minute knowledge of the detailed structure of an air package in terms of air pollution? I'm quite aware that it would be interesting to know the density distribution of all of the molecular species in a package of air at any one time for academic reasons. But I fail to see, at this stage at any rate, any reason for excessive efforts in attempting to resolve the exact condition of molecules in packages.

DR. MCKEE: Well, in the practical control program, or as a device for control uses, I don't see much use for it. I'm suggesting it primarily as an academic approach which might help in a better understanding of some of the diffusion phenomena that occur. This in turn might lead to a better understanding of the entire meteorological problem, which at the present seems to be rather poorly defined in some respects.

DR. MALONE: I'd like to say that this has application. You're right. This is an academic problem. This is basic knowledge. This has application to a lot of other meteorological problems besides air pollution. This has application to the whole problem of the general circulation because it's the kind of eddies, which you talk about, which are the mechanism by which momentum, heat, and moisture are exchanged between the atmosphere and the earth-ocean system.

DR. MCKEE: There may be more going on in that field than I know about, of course.

DR. MALONE: And there will be more in the next five years.

**MR. LAPPLE:** I'd like to cite a case which illustrates a need for information such as Dr. McKee suggests, and also represents a direct practical application. In the case of odors we have reason to believe, based on a number of instances although not conclusive, that an understanding of the detailed structure of relatively small segments may be a very important factor in odor control. You may get a whiff of odor, for example, that lasts a tenth of a second and comes by as a concentrated mass. It gives you a sensation. Maybe you do not get another one for several more seconds, but the sensation you received is sustained. I'm not a physiologist, so I do not know what time elements are required, but, by getting an average concentration that may be way below the odor threshold, you may still get the sensation of odor because of instantaneous peaks. The reason for our feeling is that we have had a number of occasions where odors have been observed at places where it was not possible to conceive of concentrations being anywhere near the odor limits.

The practical aspect of this is this: Let us assume that this explanation is correct. It then alters our thinking in stack design. The customary stack design neglects concentration in the stack because the ultimate mixing in the atmosphere is so large already, compared to the air in the stack, that it just doesn't matter how much more air you put up the stack. But in terms of these parcels of concentrated matter, by dilution at the stack, you may radically drop these peak levels at ground elevation. Here is an example of where this micrometeorology may have a very direct practical significance.

**DR. MCKEE:** This odor phenomenon that you have just mentioned is something we have also observed and this is one of the reasons why we are interested in this whole subject. We have measured $SO_2$, for example, at one- or two-tenths of a part per million, which is way below what is thought to be the odor threshold. But the fellows who were making these measurements said they could smell it. This led us to speculate that they were smelling intermittent parcels of air which came by at a higher concentration but, by chemical measurement, we were measuring the overall average for a sampling time of several minutes.

**FROM THE FLOOR:** I had two comments on the general subject of controls. In the engineering discussion there was quite a bit of attention given to the very careful specification of particle characteristics, and a very careful evaluation of washing processes, and so on. I didn't hear very much said about the specification of allowable output, other than the fact that when you have a lawsuit you have an incentive for reducing contaminants. But we must be practical as to what we can demand of a removal system. To the extent that 100 percent removal is unattainable, seems to me that the practical goal has to be established as some standard concentration in the environment, considering the dilution process from the stacks to the environment. I wonder if enough attention is being given to the relations between these goals and the design of suitable equipment.

The other comment that I had in mind was with respect to the goals of surveys and sampling studies. I think there is a danger that sampling programs may be carried out before the goals have been well-enough thought out. When the data come in they may not fit into their proper places and you might end up with just a pile of data. It is a little more involved in time to do the thinking before the collection of the samples, but it is worthwhile. Also, with regard to the sampling program itself, if you use the automatic methods of processing and techniques of statistical analyses, you may actually end up with a savings of time and get much more useful information than if you just start right in and use high-powered sampling methods indiscriminately. If you really don't know the goal of the analyses, it doesn't matter how fancy or automatic the method of processing is or how high-powered your statistical techniques are, you still won't get the answer to the problem you want. Since nobody else has mentioned these things, I thought it would be well to bring this in because it is tied together with many of the disciplines.

**DR. LODGE:** Two comments. First, to Mr. Lapple's remarks on the subject of hunks of concentration. I have a suspicion that possibly other physiological phenomena may not be proportional to the long term mean. It's nothing but a seat-of-the-pants feeling but I wonder if we can defend, at this point, the statements that the long period mean is the only significant measure of physiological response to a particular physiologically active agent.

DR. CHAMBERS: Well, Jim, in the absence of evidence I don't think we can defend either at this point.

DR. LODGE: If this is correct, I wonder if this does not point to the need for some evidence.

DR. CHAMBERS: If you mean that simple lack of information is the justification, on an academic basis, I agree with you. I'm trying to relate this to recognizable applicability in air pollution control programs. I'd like to apologize for riding the fence because I'd rather be with the academic, but we have a practical job here and have limited resources with which to accomplish it.

DR. LODGE: The other point that I wanted to raise is in regard to this list of specifications for tracers. It seems to me that in many cases these are admirably met by isotopically tagged materials--not necessarily radioactive. In many cases, tagging can be done with uncommon stable isotopes that will model most beautifully the behavior of precisely the species we've been trying to study.

DR. MALONE: Well, this is good news. We're not entirely without these; Dr. Hilst has been working with fluorescent pigment. But we end up with the thought: "We probably have something, but we'd just be delighted to know more about other trials." You have not only the scientific or technical aspect but you also have the economical aspects. We're talking about quite a few samplings and the economics has come in. This is the type of thing we'd like to know more about.

**DR. S. B. SMITH:** I think one point might be brought up here. It seems to be more strikingly evident as the conference goes on that perhaps there needs to be prepared at frequent intervals definitive statement of the present state of the art which can be disseminated to the various disciplines. The need for such information is implied by the nature of the desired information that is brought to light in these reports. I think there is a lot of information already known which we in our various pursuits cannot take into consideration. We don't have the time to read, or even to find, all the available information. Perhaps some of the abstracts and summaries should be made more easily obtainable.

**FROM THE FLOOR:** I'd like to raise a question. This relates to the integration of information. It is my understanding that laws are now being put on the books of states and cities, etc. relating to this general topic of air pollution. Is attention being directed to the gathering of pertinent materials so that when the legislators do get hold of it, there will be more reasonable laws put on the books?

**DR. WEICKMANN:** I would like to add to the report of Dr. Malone. Under certain special weather conditions we should be able to artificially precipitate some pollutants of the atmosphere. Such weather conditions occur during winter in moderate climates and result in the formation of extended, subcooled, stratus cloud decks. These clouds can be seeded artificially from aircraft with dry ice on silver iodine. Consequently, ice crystals form and the water diffuses from the liquid cloud droplets to the artificially created ice crystals. Air pollutants in the air are taken along with the water and deposited on the ice crystals. The ice crystals, falling at a rate of 1/2 to 2 meters per second, would carry the pollutants down to the ground. An area of 50 square miles can be cleared using approximately 300 to 500 pounds of dry ice.

**DR. GOETZ:** I wanted also to refer to the subject of Dr. McKee's remark. The reliability of our spot sample depends on our judgment of the "micro-inhomogeneity" of the atmosphere, both in general and in each particular test; i.e., on the magnitude of topical concentration gradients... otherwise we really don't know how representative our results are, and how large the sample has to be - or the sample area. It is the same concern a water bacteriologist has with the MPN (most probable number) problem. Most of our sampling methods use comparatively small volumes. How representative is the volume which is measured at a particular sampling station, when results can be quite different a half a block away? Rather too little attention has been paid to the probability of such variations. We cannot calculate the effects of gas and eddy diffusion, neither of micro-convection.

Very informative on this point is the extended work being done by Dr. Duntley at Point Loma on the topical variation of visibility. It certainly proves the point of atmospheric inhomogeneity. Some of the results made me realize how wrong one can be if one measures at the wrong spot or time - what is the "right" spot just at that time when you take the measurement? I believe this is a question of quite practical importance.

**DR. CHAMBERS:** If one measures in only one spot, how can we know that it is the wrong measurement?

**DR. GOETZ:** I'd just say what is the probability that you're wrong?

**DR. CHAMBERS:** In other words, you have to have a multiplicity of measurements to determine what the probable mean in that situation is in order to determine the error in one measurement. That implies that in order to make this measurement to arrive at an estimate of the error of a single measurement, you've got to make the integrated measurement any way.

**DR. HILST:** We have made a few measurements of long-term versus short-term concentrations in connection with a practical problem of acute versus chronic exposure. Our averaging times were one minute and one hour in this comparison. We found the ratio of short-term to long-term average concentrations generally fell between 10 and 30.

**MR. GRUBER:** Where were those measured, Glen? Close to the source or at some distance?

**DR. HILST:** These observations were made within one-half mile from the source.

**DR. GIFFORD:** Meteorologists have always been well aware of small scale atmospheric fluctuations purely as interesting things that go on in the air. The fact that others in the pollution field are now suggesting that concentration fluctuations may be quite as important as the mean concentration values, for some pollution problems, is very interesting. The proposed large scale experimental program described by Dr. Malone would be a good opportunity to get measurements of concentration fluctuations.

**MR. WHITBY:** I think that much of this discussion in the last hour has pointed up the common dilemma in the development of instrumentation and techniques of measurements, and that is: Where is the line to be drawn in compromising this degree of accuracy, using the term loosely, with simplicity? In other words, how much speed should you trade for cheapness? For instance, these instruments which take very rapid samples are usually very expensive. You can't use very many of them in very many places because when you have an instrument that is cheap enough to use in very many places, usually you've traded sufficient accuracy for lower cost and as a result you have another problem. I think that this is where there needs to be some general agreement and specification, particularly by people, such as the engineers, who want to use these things as to just exactly where the line should be drawn. This is not likely to be an easy thing to do.

**MR. STERN:** The gentleman who is going to have the last word, and I think this is very appropriate, is Dr. Thomas.

**DR. THOMAS:** I've had a great deal of experience with a large number of automatic analyzers spread over a considerable area. The discussion of the last few minutes has indicated very pointedly that the type of record you get depends, or should depend, on what you want to accomplish. In the measurement of an odor, if one whiff may make a person uncomfortable, then that becomes very important.

On the other hand, in considering, for example, agricultural effects of sulfur dioxide, we are interested in averaging the $SO_2$ over a considerable period of time from 30 minutes to several hours. Short time peaks have very little significance and so it seems to me to be highly important to consider the type of results that you want; the purposes for which you are collecting - using these automatic methods. Particularly I'd like to point out that when these instruments are spread over a considerable area, they actually represent the average concentrations with a great deal of accuracy. Because, when we integrate the samples over a period of time we find that the concentration actually measured, say a mile from another instrument, is just about what you'd expect it to be using the classical laws of diffusion. In one test, two $SO_2$ analyzers were operated for over a year, both at five miles from the source and 0.4 miles apart. The summation of all the 30-minute average concentrations on the two recorders over this period agreed within less than one percent. Shorter time comparisons - monthly, weekly, daily, and even hourly - were generally remarkably concordant also. So it seems to me that it's not so important to have a great number of these recorders, but to have them placed to represent concentrations over a considerable area. Even though a particular fumigation may not record on a particular recorder, the recorder at that spot will still represent the actual average concentration, the average level, that occurs over a wide area. So I think, that in actual practice, a great deal of simplicity is possible in this field which isn't so evident when you begin to look at in in a very micro way.

**MR. STERN:** That was really a fine conclusion for all of these discussions. Having witnessed the quality of the discussions on the concluding day, I can only regret that I was absent on the first day and didn't hear the equal words of wisdom.

When we ran this Air Pollution Research Planning Seminar for the first time in 1956, we were very much feeling our way and we made a lot of mistakes. Afterwards we sent letters to all of the participants asking for a critique of the sessions in order that we might improve our performance the next time around. We've tried to use as many as possible of the constructive criticisms that were offered us, as a result of the 1956 session, in planning the 1958 session. It seems obvious, I believe, that another session, at a year as yet unnamed, would be desirable. Whether this should be a year from now, two years from now, or whatever the time interval should be, would have to rest largely on the critique that this group offers. We will do as we did in the original session; send you, within a reasonably short time, a letter requesting your critique of this session and asking for your advice as to how any similar session might be improved if we hold it in the future. We'll also ask you if you think another such session should be held, when, where, similar questions to those we asked after the '56 session and which helped us to lay the ground work for this one.

I have heard a discussion that perhaps there should be an alternating form of program -- a research planning seminar in even years and some other form of get-together in odd years. These are the things on which we would like your advice. As we get to the magic hour of 12:30, I want to first thank all of the chairmen for the extra-onerous duties they undertook to make this a success: Thanks to the committee members for staying up late and working so hard: to Ron Evans for having recorded this session, and to Don Keagy for all the work he has done, in organizing and running this seminar. The seminar is adjourned.

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# ATTENDANCE

## Second
## Annual Research Planning Seminar

February 3,4, and 5, 1958
Cincinnati, Ohio

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